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(54) Title: A METHOD OF TREATING DISORDERS RELATED TO CYTOKINES IN MAMMALS

(57) Abstract

A method of treating disorders related to cytokines such as TNFα in mammals. The disorder is an autoimmune disorder, inflammation, arthritis, type I or type II diabetes, multiple sclerosis, stroke, osteoporosis, septic shock or menstrual complications.

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A method of treating disorders related to cytokines in mammals

Field of the invention

The present invention relates to a method of treating disorders related to cytokines in humans, including autoimmune disorders, inflammation, arthritis, type I or type II diabetes, multiple schlerosis, stroke, osteoporosis, septic shock and menstrual complications. The invention furthermore relates to the use of known and new purine derivatives for the manufacture of a pharmaceutical composition for treating the above diseases as well as new purine derivatives having affinity for subtypes of adenosine receptors and acting as cytokine inhibitors.

Background of the Invention

Adenosine receptors represent a subclass (P_1) of the group of purine nucleotide and nucleoside receptors known as purinoreceptors. This subclass has been further classified into distinct receptor types which are now known as A_1, A_{2a}, A_{2b} and A_3.

Extensive research has been carried out in a quest to identify selective ligands at these receptors [see, for example, Fredholm, B.B.; Abbracchio, M.P.; Burnstock, G.; Daly, J.W.; Harden, T.K.; Jacobson, K.A.; Williams, M. Nomenclature and Classification of Purinoceptors. *Pharmacol. Rev.* **1994**, *46*, 143-156; Van Galen, P.J.M.; Stiles, G.L.; Michaels, G. Jacobson, K.A. Adenosine A_1 and A_2 Receptors: Structure Activity Relationships. *Med. Chem. Rev.* **1992**, *12*, 423-471; Linden, J. Cloned Adenosine A_3 receptors: Pharmacological Properties, Species Differences and Receptor Functions. *TIPS* **1994**, *15*, 298-306; Jacobson, K.A.; Kim, H.A.; Siddiqi, S.M.; Olah, M.E.; Stiles, G.L.; von Lubitz, D..K.J.E.; A_3 Adenosine Receptors: Design of Selective Ligands and Therapeutic Propects. *Drugs of the Future* 1995, *20*, 689-699; Collis, M.G.; Hourani, S.M.O.; Adenosine Receptor Subtypes, *TIPS* **1993**, 360-366].

Several purine derivatives are known to modulate the release and or action of cytokines. For

example the naturally occurring 5'-methylthioadenosine has been shown to inhibit cytokine production (Cerri, M.A.; Beltran-Nunez, A.; Bernasconi, S.; Dejana, E.; Bassi, L.; Bazzoni, G. Inhibition of Cytokine Production and Endothelial Expression of Adhesion Antigens by 5'-Methylthioadenosine. *Eur. J. Pharmacol.* **1993**, *232*, 291-294).

Furthermore, the adenosine agonists *R*-PIA, NECA, CPCA, CGS 21680, 2-chloroadenosine and CHA as well as the adenosine uptake inhibitor dipyridamole have all been shown to have an inhibitory effect on Tumour Necrosis Factor (TNF) production (Le Vraux, V.; Chen, Y.L.; Masson, M.; De Sousa, M.; Giroud, J.P.; Florentin, I.; Chauvelot-Moachon, L. Inhibition of Human Monocyte TNF production by Adenosine Receptor Agonists. *Life Sci.* **1993**, *52*, 1917 - 1924) and these workers conclude that it is the A_2 adenosine receptor which is involved in this aspect of TNF inhibition. The post-receptor event is presumably upregulation of adenylate cyclase. In a separate study, the specific adenosine A_1 agonists 2-chloroadenosine and CCPA as well as the A_2 agonist CPCA have been identified as inhibitors of lipopolysaccharide-stimulated TNF-α production, with the A_2 agonist CPCA being 1000-fold more potent than CCPA, giving further evidence of the probable involvement of the adenosine A_2 receptor. These findings have been confirmed by others (Prabhakar, U.; Brooks, D.P. Lipschlitz, D.; Esser, K.M. Inhibition of LPS-induced TNF-α Production in Human Monocytes by Adenosine (A_2) Receptor Selective Agonists. *Int. J. Immunopharmac.* **1995**, *17*, 221-224).

This effect of adenosine receptor agonists on TNF biosynthesis have been reviewed recently (Lee, J.C.; Prabhakar, U.; Griswold, D.E.; Dunnington, D.; Young, P.R.; Badger, A. Low-Molecular-Weight TNF Biosynthesis Inhibitors: Strategies and Prospectives. *Circulatory Shock* **1995**, *44*, 97-103) as has their therapeutic potential (Giroud, J.P.; Lian Chen, Y.; Le Vraux, V.; Chauvelot-Moachon, L. Therapeutic Aspects of Adenosine in Relation to its anti-TNF properties. *Bull. Acad. Natl. Med. (Paris)* **1995**, *179*, 79 -101).

Disease states involving TNF-α

The suggestion has been made that TNF-α inhibitors are useful in the treatment of diabetes

(Argiles, J.M., Lopez-Soriano, J. and Lopez-Soriano, F.J. Cytokines and Diabetes: The Final Step. Involvement of TNF-α in both Type I and Type II Diabetes Mellitus. *Horm. Metab. Res.*, **1994**, *26*, 447 - 449).

It is now clear that TNF-α levels are increased in obese rodents (Yamakawa, T., Tanaka, S-I., Yamakawa, Y., Kiuchi, Y., Isoda, F., Kawamoto, S, Okuda, K. and Sekihara, H. Augmented Production of Tumor Necrosis Factor–α Production in Obese Mice. *Clin. Immunol. and Immunopath.*, **1995**, *75*, 51-56). A clinical study of the expression pattern of TNF-α in adipose tissue of obese and normal premenopausal women has been carried out (Hotamisligil, G.S., Arner, P. Caro, J.F., Atkinson, R.L. and Spielgelman, B. Increased Adipose Tissue Expression of Tumor Necrosis Factor–α in Human Obesity and Insulin Resistance. *J. Clin. Invest.*, **1995**, *95*, 2409 - 2415). Obese individuals express 2.5-fold more TNF-α mRNA in fat tissue relative to lean controls, and there was a correlation to the level of hyperinsulinemia, suggesting a role for TNF-α in the pathogenesis of obesity related insulin resistance. The topic of TNF-α in insulin resistance has been reviewed by the same group (Hotamisligil, G.S. and Spielgelman, B. Perspectives in Diabetes. Tumor Necrosis Factor–α: A Key Component of the Obesity-Diabetes Link. *Diabetes*, **1994**, *43*, 1271 - 1278).

Some investigators suggest that adenosine and adenosine agonists, acting *via* A_2 receptors can be of benefit in for example septic shock or ischaemia-reperfusion injury, where cytokine production by mononuclear phagocytes can be inhibited by these agents (Bouma, M.G., Stad, R.K., van den Wildenberg, A.J.M. and Buurman, W.A. Differential Regulatory Effects of Adenosine on Cytokine Release by Activated Human Monocytes. *J. Immunol.*, **1994**, *153*, 4159 - 4168). These effects by A_2 receptor agonists have also been demonstrated on human polymorphonuclear leukocytes (Thiel, M. and Chouker, A. Acting Via A_2 Receptors, Adenosine Inhibits the Production of Tumor Necrosis Factor–α of Endotoxin-stimulated Human Polymorphonuclear Leucocytes. *J. Lab Clin. Med.* 1995, 275 - 282).

A massive release of TNF-α in the host produces severe damage to a range of tissues. It is

therefore clear that TNF-α inhibitors have application in disorders which involve an inflammatory response, but this cytokine has multiple inflammatory, metabolic and immunological activities (Jirillo, E. Pellegrino, N.M. and Antonaci, S. Role of Tumor Necrosis Factor–α in Physiological and Pathological Conditions. *Med. Sci. Res.*, **1995**, *23*, 75-79).

Many patented TNF-α inhibitors such as rolipram, pentoxyfylline and denbufylline are phosphodiesterase (PDE) inhibitors and exert their effects on TNF-α *via* control of cAMP (Davidsen, S.K. and Summers, J.B. Inhibitors of TNF-α Synthesis. *Exp. Opin. Ther. Patents* **1995**, *5*, 1087 - 1100). Evidence is also available for some synergism between the effects of rolipram and adenosine in reduction of T primed neutrophil oxidative activity, thereby offering protection against inflammatory tissue damage (Sullivan, G., Carper, H.T. and Mandell, G.L. *Int. J. Immunopharmac.* **1995**, *17*, 793-803).

There is also good evidence for TNF inhibitors in the prevention of neuronal damage following cerebral ischaemia (Firestein, G.Z., Liu, T and Barone, F.C. Cytokines, Inflammation, and Brain Injury: Role of Tumor Necrosis Factor–α. *Cerebrovascular and Brain Metabolism Reviews* **1994**, *6*, 341-360).

Prior art

Examples of adenosine derivatives in the chemical literature with the heteroatoms, oxygen or nitrogen bonded directly to the 6-amino substituent are summarised below.

Examples with hydrogen at the purine 2-position include *N*-aminoadenosine, *N*-[(*N*-methyl-*N*-phenyl)amino]adenosine, *N*-hydroxyadenosine, *N*-methoxyadenosine and *N*-benzyloxyadenosine (Kusachi, S., Thompson, R.D. Bugni, W.J., Yamada, N. and Olsson, R.A. Dog Coronary Artery Adenosine Receptor: Structure of the N^6-Alkyl Subregion. *J. Med. Chem.*, **1985**, *28*, 1636 - 1643); *N*-ethoxyadenosine (Fujii, T., Wu, C.C., Itaya, T., Moro, S. and Saito, T. Purines. XI. The

Synthesis of *N*-Alkoxyadenosines and Their 2',3'-O-Isopropylidene Derivatives. *Chem. Pharm. Bull.*, **1973**, *21*, 1676 - 1682); (Fuji, T., W, C.C. and Itaya, T. Purines. XII. Catalytic Hydrogenolysis of Alkoxyaminopurines and Related Derivatives. *ibid.*, **1973**, *21*, 1835 -1838); *N*-(methylamino)adenosine and *N*-[(*N*-hydroxy-*N*-methyl)amino]adenosine (Giner-Sorolla, A., O'Bryant, S.A., Nanos, C., Dollinger M.R., Bendich, A. and Burchenal, J.H. The Synthesis and Biological Properties of Hydroxylaminopurines and Related Derivatives. *J. Med. Chem.*, **1968**, *11*, 521 - 523).

Examples of adenosine derivatives with oxygen or nitrogen atoms bonded to the 6-amino substituent, containing an additional purine 2-substituent are 2-amino-*N*-hydroxyadenosine (Kikugawa, K., Iizuka, K., Higuchi, Y., Hirayama, H. and Ichino, M. Platelet Aggregation Inhibitors. 2. Inhibition of Platelet Aggregation by 5'-,2-,6-, and 8-substituted Adenosines. *J. Med. Chem.*, **1972**, *15*, 387 - 390); 2-amino-*N*-aminoadenosine (Saneyoshi, M. and Terashima, K. Synthetic Nucleosides and Nucleotides. VII. A Direct Replacement of 6-Thiol Group of 6-Thioinosine and 6-Thioguanosine with Hydrazine Hydrate. *Chem. Pharm. Bull.*, **1969**, *17*, 2373 - 2376); 2-amino-*N*-methoxyadenosine (*Chem. Pharm. Bull.*, **1975**, *23*, 464 - 466); (Ueda, T., Miura, K. and Kasai, T., Synthesis of 6-Thioguanosine and 2,6-diaminopurine Nucleosides and Nucleotides from Adenosine Counterparts via a facile Rearrangement in the Base Portion (Nucleosides and Nucleotides XIX). *Chem. Pharm. Bull.*, **1978**, *26*, 2122 - 2127); 2-chloro-*N*-hydroxyadenosine (Cristalli, G., Sauro, V., Eleuteri, A., Grifantini, M., Volpini, R., Lupidi, G., Capolongo, L. and Pesenti, E. Purine and 1-Deazapurine Ribonucleosides and Deoxyribonucleosides: Synthesis and Biological Activity. *J. Med. Chem.*, **1991**, *34*, 2226 - 2230); (IJzerman, A.P. von Frijtag Drabbe Kunzel, J.K., Vittori, S. and Cristalli, G. Purine-Substituted Adenosine Derivatives with Small N^6-Substituents as Adenosine Receptor Agonists. *Nucleosides and Nucleotides*, **1994**, *13*, 2267 - 2281): 2-fluoro-*N*-hydroxyadenosine and 2-fluoro-*N*-aminoadenosine (Montgomery, J.A. and Hewson, K. 2-Fluoropurine Ribonucleosides. *J. Med. Chem.*, **1970**, *13*, 427 - 430) and 2-fluoro-*N*-methoxyadenosine (Giner-Sorolla, A. and Burchenal, J.H., Substituted Hydroxylaminopurines and Related Derivatives. Synthesis and Screening Tests. *J. Med. Chem.*, **1971**, *14*, 816 - 819).

(1R,4S)-9-[4-(Dimethylthexylsilyloxymethyl)cyclopent-2-enyl]-6-methoxyamino-9H-purine-2-amine is featured as an intermediate in the synthesis of (-)-carbovir (Exall A.M., Jones, M.F., Mo, C-L., Myer, P.L., Paternoster, I.L., Singh, H., Storer, R., Weingarten, G.G., Williamson, C., Brodie, A.C., Cook, J., Lake, D.E., Meerholz, C.A., Turnbull, P.J. and Highcock, R.M. Synthesis from (-)-Aristeromycin and X-Ray structure of (-)-Carbovir. J. Chem. Soc. Perkin Trans. I, 1991, 2467 - 2477). A related purin-2-amine is featured as an intermediate in the synthesis of the antiherpetic agent carbocyclic 9-(2'-deoxy-2'-fluoro-b-D-arabinofuranosyl)guanine (Borthwick, A.D., Biggadike, K., Holman, S. and Mo, C-L., Enantiospecific Synthesis of the Potent Antiherpetic Carbocyclic 9-(2'-deoxy-2'-fluoro-b-D-arabinofuranosyl)guanine (+)-C-APG from Aristeromycin. Tetrahedron Lett., 1990, 31, 767-770).

Some of the biological effects of the compounds contained within this application on the central nervous system have been published (Knutsen, L.J.S., Lau, J., Eskesen, K., Sheardown, M.J., Thomsen, C., Weis, J.U., Judge, M.E. and Klitgaard, H. Anticonvulsant Actions of Novel and Reference Adenosine Agonists. In *Adenosine and Adenine Nucleotides: From Molecular Biology to Integrative Physiology*, Belardinelli, L. and Pelleg, A., Eds.; Kluwer: Boston, MA; **1995**, 479-487. See also Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; The Synthesis and Biochemical Evaluation of New A_1 Selective Adenosine Receptor Agonists Containing a 6-Hydrazinopurine Moiety; *BioMed. Chem. Lett.*, **1993**, *3*, 2661-2666).

In the above scientific articles, no mention is made of any pharmacological effects of the compounds concerned which can be ascribed to cytokine modulation.

The recent patents within novel purinergic agents has been reviewed (Bhagwhat, S.S.; Williams, M. Recent Progress in Modulators of Purinergic Activity. *Exp. Opin. Ther. Patents* **1995**, *5*, 547 - 558), as have patents covering TNF inhibitors (Davidsen, S.K. and Summers, J.B. Inhibitors of TNF-α Synthesis. *Exp. Opin. Ther. Patents* **1995**, *5*, 1087 - 1100).

Marion Merrell Dow Inc. has claimed some cyclopentyl substituted adenines which appear to exert their effects by control of TNF-α (US 5,244,896). A follow-up application by Merrell Dow Pharmaceuticals Inc. (WO 95/03304) disclosed some novel bicyclic 9-bicyclic nucleosides useful as selective inhibitors of proinflammatory cytokines.

Merck & Co. Inc. has filed a patent application claiming a method for inhibiting TNF-α production comprising contacting the A_{2b} subtype of the adenosine receptor with an adenosine agonist (GB 2289218-A).

Some other purine derivatives which are TNF inhibitors, presumably owing to their activity as PDE inhibitors, have been reviewed (This Years Drug News. Cardiovascular Drugs. Treatment of Septic Shock 1994 pp 185 - 189).

In WO 9533750-A1, Pfizer Inc. claim a range of heterocycles, including some purine derivatives, as CRF antagonists.

In US Patent 3,819,613, substituted adenosine analogues with hydrazone derivatives on the 6-amino function are disclosed as hypotensive agents. In GB 1,351,501, adenosine and 2-amino-adenosine derivatives having a -NH-R_2 group joined to the 6-amino function are disclosed as coronary dilators and platelet aggregation inhibitors. In EP A 152,944, a series of 2-, 6- and 8-substituted adenosine derivatives are described having activity as anti-allergy agents. In EP 402,752A, derivatives of adenosine unsubstituted in the 2-position are described which have a substituted heteroaromatic 1-pyrrolyl moiety attached to the 6-amino group.

There are only relatively few examples where the ribose moiety in adenosine is chemically modified, and many of those known have poor affinity for the adenosine receptor (Taylor, M.D., Moos, W.H., Hamilton, H.W. Szotek, D.S. PAtt, W.C. Badger, E.W. Bristol, J.W. Bruns, R.F. Heffner, T.G. Mertz, T.E. Ribose-Modified Adenosine Analogues as Adenosine Receptor

Agonists. *J. Med. Chem.*, **1986**, *29*, 346-353).

However, minor modifications at 3'- and 5'- appear to be allowed and amongst these the 5'-chloro-5'-deoxy adenosines show particularly good receptor affinity (Trivedi, B.K., Bridges, A.J., Patt, W.C. Priebe, S.R., Bruns, R.F. N^6-Bicycloalkyladenosines with Unusually High Potency and Selectivity for the Adenosine A_1 Receptor *J. Med. Chem.*, **1989**, *32*, 8-11). Other scientific articles also describe 5'-modifications of adenosine derivatives (Olsson, R.A. Kusachi, S., Thompson, R.D., Ukena, D., Padgett, W. and Daly, J.W. N^6-Substituted N-Alkyladenosine-5'-uronamides: Bifunctional Ligands Having Recognition Groups for A_1 and A_2 Adenosine Receptors. *J. Med. Chem.*, **1986**, *29*, 1683-1689).

Many of the new adenosine A_3 receptor agonists are 5'-modified adenosine derivatives (Jacobson, K.A.; Kim, H.A.; Siddiqi, S.M.; Olah, M.E.; Stiles, G.L.; von Lubitz, D..K.J.E.; A_3 Adenosine Receptors: Design of Selective Ligands and Therapeutic Propects. *Drugs of the Future* 1995, *20*, 689-699; Baraldi, P.G., Cacciari, B., Spalluto, G. Ji, X-d, Olah, M.E. Stiles, G., Dionsiotti, S., Zocchi, C., Ongini, E. and Jacobson, K.A. Novel N^6-(Substituted-phenylcarbamoyl)adenosine-5'-uronamides as Potent Agonists for A_3 Receptors. *J. Med. Chem.*, **1986**, *39*, 802-806).

EP-A-181,128 and EP-A-181,129 disclose 5'-deoxy adenosine derivatives containing 5'-hydrogen, 5'-halogen and 5'-methylthio, which are claimed to have desirable anti-inflammatory, analgesic as well as CNS and antihypertensive properties respectively.

EP-A-232,813 discloses *N*-substituted adenosines including a larger range of 5'-modified compounds. In WO 88/03147 5'-substituted adenosine derivatives with selectivity for the adenosine A_2 receptor are disclosed.

In US 4,962,194 methods for preparing 5', N^6-disubstituted adenosine derivatives are revealed. GB 1,101,108 discloses 5', N^6-disubstituted adenosine analogues which possess cardiovascular activity. US Patent No. 3,910,885 reveals 4'-alkoxy and 4'-haloalkoxy nucleosides. PCT

publication WO 94/06348 discloses a number of pyrrolo[3,4-d]pyrimidine structures which are formally isosteric with adenosine and which are modified at the sugar 5'-position. US Patent No. 5,308,837 covers the use of 5'-amine substituted adenosine analogues as immunosupressants.

In EP Publication No. 0 423 777 A2 a method for treating gastrointestinal motility disorders using N(6) (substituted aminoalkyl) adenosine derivatives is disclosed. EP Publication No. 0 490 818 A1 describes a new use of 2'-O-methyl adenosine derivatives for a range of ailments including neurodegenerative disorders.

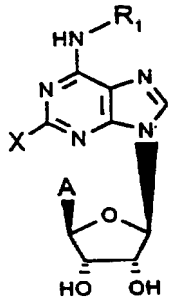
In WO 93/23417 (corresponds to US patent No. 5,430,027) and WO 95/07921 adenosine derivatives having central nervous system (CNS) properties are disclosed.

According to the present invention the compounds of WO 93/23417 and WO 95/07921 and some closely related compounds have been found to be cytokine inhibitors, for example inhibitors of TNF-α, and are found to be useful in the treatment of disorders related to cytokines in mammals, including humans. These conditions include inflammation, arthritis, type I and type II diabetes, autoimmune disorders, multiple schlerosis, stroke, osteoporosis, septic shock and menstrual complications.

Description of the invention.

Thus the present invention relates to a new use of adenosine analogues containing both ribose and modified ribose moieties, some of which are disclosed in WO 93/23417 and WO 95/07921, which show potent binding to adenosine receptors.

More specifically the present invention relates to a method of treating disorders related to cytokines in mammals comprising administering to a mammal in need thereof an effective amount of a compound of the general formula (I), or a pharmaceutically acceptable salt thereof:



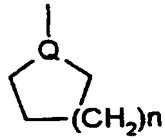
(I

wherein

X represents hydrogen, halogen, amino, perhalomethyl, cyano, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino or phenyl;

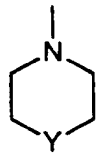
A is hydroxymethyl, methyl, chloromethyl, bromomethyl, fluoromethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl;

R_1 is selected from the groups consisting of



(a)

wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy- C_{1-6}-alkyl, phenylthioalkyl or

(b) 

wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

R^1 is $-NR^2R^3$ or $-YR^4$,

wherein Y is oxygen;

R^2 is C_{1-6}-alkyl;

R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;

R^4 is straight-chain C_{1-6}-alkyl, branched C_{3-8}-alkyl, C_{2-8}-alkenyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

A preferred method of treating disorders involving cytokines comprises administering to a subject in need thereof a compound of the above general formula (I) wherein R^1 is $-OR^4$, wherein R^4 is straight-chain C_{1-6}-alkyl, branched C_{3-8}-alkyl, C_{2-8}-alkenyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

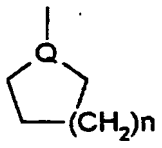
The present invention is furthermore concerned with new compounds of the above formula (I) or pharmaceutically acceptable salts thereof, wherein

X represents phenyl;

A is hydroxymethyl, methyl, chloromethyl, bromomethyl, fluoromethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl;

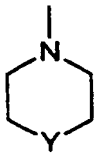
R_1 is selected from the groups consisting of

(a)



wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, phenylthioalkyl or

(b)



wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

R^1 is $-NR^2R^3$ or $-YR^4$,

wherein Y is oxygen;

R^2 is C_{1-6}-alkyl;

R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;

R^4 is straight-chain C_{1-6}-alkyl, branched C_{3-8}-alkyl, C_{2-8}-alkenyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

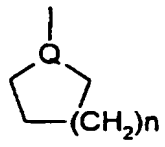
The present invention is furthermore concerned with new compounds of the above formula (I) or pharmaceutically acceptable salts thereof, wherein

X represents hydrogen, halogen, amino, perhalomethyl, cyano, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino or phenyl;

A is hydroxymethyl, methyl, chloromethyl, bromomethyl, fluoromethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl;

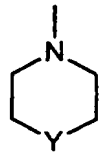
R_1 is selected from the groups consisting of

(a)



wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy- C_{1-6} -alkyl, phenylthioalkyl or

(b)



wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

R^1 is $-NR^2R^3$ or $-YR^4$,

wherein Y is oxygen;

R^2 is C_{1-6}-alkyl;

R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;

R^4 is branched C_{3-8}-alkyl or C_{2-8}-alkenyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

Various salts of compounds of formula (I) can be prepared which can be considered physiologically acceptable. These include addition salts derived from inorganic or organic acids, for example, acetates, fumarates, glutarates, glutaconates, lactates, maleates, methanesulphonates, phosphates, salicylates, succinates, sulphates, sulphamates, tartrates and paratoluenesulphonates. In some cases, solvates of either the free nucleosides or the acid addition salts can be isolated and these solvates may, for example, be hydrates or alcoholates.

It has been found that the compounds of formula (I) have affinity for subtypes of adenosine receptors, modulate cyclic AMP and act as cytokine inhibitors. Moreover, these compounds are found to be useful as drugs in the treatment of disorders where damaging effects of cytokines are observed in humans.

Evaluation of these compounds in established animal models has indicated that the compounds according to the invention possess desirable pharmacological properties which can be ascribed to cytokine modulation. For example they inhibit TNF-α synthesis, as indicated by lowering of plasma TNF-α following lipopolysaccharide (LPS) challenge in rats.

Evaluation of *in vitro* binding to adenosine A_1 and A_{2a} receptors

The affinity of the compounds described in this invention for the adenosine A_1 receptor was

determined essentially as described in the literature using [^{3}H]-*R*-PIA as a radioligand (Naunyn-Schmiedeberg's Archives of Pharmacology, **1980**, *313*, 179-187). Affinity for the A_{2a} receptor was measured using the radioligand [^{3}H]-CGS 21680 (European Journal of Pharmacology, **1989**, *168*, 243-246).

Evaluation of *in vitro* binding to adenosine A_3 receptors

An assay for the human adenosine A_3 receptor is described in Jacobson, M. Cloning and Expression of Human Adenosine Receptor Subtypes. In *Adenosine and Adenine Nucleotides: From Molecular Biology to Integrative Physiology*, Belardinelli, L. and Pelleg, A., Eds.; Kluwer: Boston, MA; 1995, pp 5-13.

[^{125}I]-AB-MECA binding to adenosine A_3 receptors

The adenosine receptor subtype A_3 has been expressed in a human embryonic kidney cell line (HEK 293) and shown to be negatively coupled to adenylate cyclase *via* a pertussis toxin sensitive G-protein. When the A_3 receptor is expressed in CHO cells, it has been shown that [^{125}I]-AB-MECA binds with a high affinity to this receptor A_3 (K_i = 1.5 nM) (Linden, J. Trends Pharmacol. Sci. 1994, 15, 298).

Method

HEK 293 cells were cultured in Dulbecco's modified Eagles media supplemented with 10% fetal bovine serum, 2 MM glutamine, 0.1 mg/mL streptomycin, 0.1 mg/mL penicillin and 0.8 mg/mL G418 in an incubator at 37°C (95% air, 5% CO_2). HEK 293 cells were seeded in 24-well plates two days before the experiment so that they were 70-80% confluent on the day of the assay. Cells were washed twice with 1 mL of assay buffer (the composition was: 118 mM NaCl, 25 MM $NaHCO_3$, 4.7 mM KCl, 1.2 mM KH_2PO_4, 1.2 mM $CaCl_2$, 3.8 mM $MgCl_2$, 1.2 mM $MgSO_4$, 11 mM D-glucose and 10 mM HEPES, pH 7.4). The cells were

subsequently incubated for 15 min at 37°C in assay buffer supplemented with 2 U/mL adenosine deaminase. Test compounds or buffer were added to the cells before [^{125}I]-AB-MECA and incubated for 45 min. at 37°C in a final volume of 500mL. The cells were washed quickly with 2 x 2 mL ice-cold assay buffer, solubilised with 1 mL of NaOH (2 M) and transferred to g-counting vials with 0.5 mL water.

Test procedure & data analysis

Test compounds are dissolved in DMSO, ethanol or water and further diluted in assay buffer. The final concentrations of solvents should be less than 2%. Test solutions should be in the range of pH 6.5 - 7.5. IC_{50} values were calculated from dose-response curves (3 points minimum) by a non-linear regression analysis using the GraphPad Prism program (GraphPad Software, USA). The results expressed in nM.

***In vitro* assay of TNF-α**

The test compound is dissolved in dimethyl sulphoxide (DMSO) at 8 mg/mL and is diluted with Cremophor in 5% saline (0.9% aqueous NaCl) to 160, 16 and 1.6 μg/mL. 25 μL is added to each tube, and 350 mL heparinised (50 iE/mL) rat blood, 25 μL lipopolysaccharide (LPS) 1.6 mg/mL in saline are introduced, i.e. the concentrations of the test compound is 10, 1 and 0.1 mg/μL respectively. The samples are shaken carefully and are placed in a water bath for 5 h. at 37°C. The samples are centrifuged for 10 min. at 3000 rpm at 4°C. The plasma is removed by pipette in plastic tubes and is frozen. TNF-α levels are determined using a Genzyme ELISA kit.

Biological activity of selected examples *in vitro*

Example number	Inhibition of rat brain ^{3}H-R-PIA binding K_i (nM) A_1	Inhibition of rat brain ^{3}H-CGS 21680 binding K_i (nM) A_{2a}	Inhibition of rat brain K_i (nM) A_3	Ratio A_1/A_3	LPS-induced TNF-α inhibition rat whole blood IC_{50} (μM)
8	15	4500	10.4	1.5	3.0
34	170	13000	26.3	6.5	0.9
43	100	9500	4.6	22	3.0
50	1230	63400	20.2	61	0.9
N-benzyl MECA	2400	2100	41	58	3.0

Pharmaceutical compositions

The compounds of the invention, together with a conventional adjuvant, carrier or diluent, and if desired in the form of a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets of filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral use (including subcutaneous administration and infusion). Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the adenosine receptor agonist commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, ten (10) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparation, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilised and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets, dragees, or capsules having talc and/or carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir or the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05-100 mg in

a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1-300 mg/day, preferably 10-100 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

Active compound	5.0 mg
Lactosum	67.0 mg Ph.Eur.
Avicel™	31.4 mg
Amberlite™IRP 88	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

Owing to activity against inflammation, arthritis, diabetes, multiple schlerosis, stroke, osteoporosis, septic shock, menstrual complications and autoimmune disorders the compounds of the invention are extremely useful in the treatment of related symptoms in mammals, when administered in an amount effective for agonist activity of compounds of the invention. The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of adenosine receptor agonist, and if desired in the form of a pharmaceutically acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulphate), in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective amount of adenosine receptor agonist, and in any event an amount which is effective for the treatment diseases related to cytokines, owing to their adenosine receptor agonist activity. Suitable dosage ranges are 1-200 milligrams daily, 10-100 milligrams daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is

directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The preparation of compounds of the invention is further illustrated in the following examples.

Hereinafter, TLC is thin layer chromatography, THF is tetrahydrofuran, TFA is trifluoracetic acid and m.p. is melting point. Where melting points are given, these are uncorrected. The structures of the compounds are confirmed by assignment of NMR spectra (from which representative peaks are quoted) and by microanalysis where appropriate. Compounds used as starting materials are either known compounds or compounds which can be prepared by methods known per se. Column chromatography was carried out on Merck silica gel 60 (Art 9385). HPLC was carried out on a Waters or Merck chromatograph with a multiwavelength detector and a reversed phase C18 column (250 x 4 mm, 5mm, 100Å; eluent flow rate 1 mL/ min at 35°C). Retention times are given in minutes.

Examples

EXAMPLE 1

2-Chloro-*N*-(*N*-methyl-*N*-(2-phenylethyl)amino)adenosine.

N-Methyl-2-phenylethylamine hydrochloride.

Phenylacetaldehyde (24.0 g, 0.20 mol), a 33% solution of methylamine in ethanol (42.35 g, 0.41 mol) and methylamine hydrochloride (10.13 g, 14.8 mmol) were dissolved in methanol (200 mL). Sodium cyanoborohydride (3.77 g, 60 mmol) was introduced and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was evaporated in vacuo to ca. 50 mL, concentrated hydrochloric acid (40 mL) was added and once the exotherm had subsided the reaction mixture was stirred for 2 h. Water (200 mL) was introduced followed by potassium

hydroxide (27g, 0.48 mol) and the cooled solution was extracted with dichloromethane (7 x 100 mL). The combined dichloromethane extracts were extracted with 2 N hydrochloric acid solution (200 mL) and 0.2 N hydrochloric acid solution (200 mL). The combined acidic extracts were washed with dichloromethane (2 x 50 mL) and the aqueous phase was basified with 4 N sodium hydroxide solution before being extracted with dichloromethane (2 x 100 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue (9.2 g) which was dissolved in toluene (200 mL) with methanol (5 mL) present. Chlorotrimethylsilane (8.63 mL) dissolved in toluene (300 mL) was added and the hydrochloride salt of *N*-methyl-2-phenylethylamine precipitated. After cooling the suspension, the solid was collected by filtration and dried in vacuo; ^1H NMR (DMSO-d_6) d 2.54 (3H, s, -CH_3), 2.92-3.07 (4H, m, -CH_2CH_2-), 7.20 -7.40 (5H, m, Ar-H).

N-Methyl-*N*-nitroso-2-phenylethylamine

A sample of *N*-methyl-2-phenylethylamine hydrochloride (6.4 g, 37.3 mmol) was dissolved in water (18 mL), ethanol (11 mL) and 2 N hydrochloric acid (4 mL) were introduced and the solution was heated to 70°C. A solution of sodium nitrite (2.6g, 37.7 mmol) in water (11 mL) was added dropwise to the reaction mixture over 30 min. During the addition the reaction mixture was acidified with 2 N hydrochloric acid (4 mL). Cooling was followed by extraction with n-heptane (4 x 100 mL); the combined extracts were dried ($MgSO_4$) and evaporated in vacuo to provide the *N*-methyl-*N*-nitroso-2-phenylethylamine as an oil (5.0 g, 81%) (a ca. 65:35 mixture of apparent geometric isomers), ^1H NMR (DMSO-d_6)d 2.98 (3H, s, -CH_3), 3.05 (2H, t, $PhCH_2$-), 4.37 (2H, t, -CH_2-N-), 7.13-7.36 (5H, m, Ar-H) (major isomer); 2.78 (2H, t, $PhCH_2$-), 2.98 (3H, s, -CH_3), 3.77 (2H, t, -CH_2-N-), 7.13-7.36 (5H, m, Ar-H) (minor isomer).

1-Methyl-1-(2-phenylethyl)hydrazine.

The above nitrosamine (5.0 g, 30.4 mmol) was dissolved in dry THF (100 mL) and a 1 M solution of lithium aluminium hydride in THF was added dropwise. On heating to 55°C reaction

commenced, the mixture was heated at reflux for 30 min. and cooled to room temperature. The reaction mixture was kept cool using a 23°C water bath and water (50 mL) was carefully introduced dropwise with rapid stirring, followed by 1N sodium hydroxide solution (4 mL). The precipitate was removed by filtration and the filtrate was extacted with dichloromethane (3 x 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to a residue (4.08 g) which was dissolved in toluene (100 mL) with methanol (2 mL) present. Chlorotrimethylsilane (3.46 mL) dissolved in toluene (200 mL) was introduced and the hydrochloride salt of 1-methyl-1-(2-phenylethyl)hydrazine was separated as a gum, ^{1}H NMR ($CDCl_3$) d 2.44 (3H, s, $-CH_3$), 2.56 (2H, t, $-CH_2$), 2.76 (2H, t, $-CH_2$), 3.36 (2H, br s, $-NH_2$), 7.13 - 7.32 (5H, m, Ar-H).

9-(2',3',5'-tri-*O*-Benzoyl–β–D-ribofuranosyl)-2,6-dichloro-9H-purine

2,6-dichloro-9H-purine (5.8 g, 30.7 mmol) and 1-*O*-acetyl-tri-*O*-benzoyl–β–D-ribofuranose (16.26 g, 32.2 mmol) were thoroughly mixed (as powdery solids) and fused together at 145-150°C under oil pump vacuum. The resultant oily mixture was stirred gently for 0.75 h (during which time the acetic acid by-product evaporated) and cooled to ca. 50°C before being dissolved in dichloromethane (100 mL) with stirring. This solution was applied directly to a column of silica gel (6 x 22 cm) and eluted initially with cyclohexane/dichloromethane (1/1), then with dichloromethane and finally with cyclohexane/ethyl acetate (1/1) to provide 9-(tri-*O*-benzoyl–β–D-ribofuranosyl)-2,6-dichloro-9H-purine (16.6 g, 87%) as a colorless foam, TLC rf 0.50 [SiO_2, cyclohexane/ ethyl acetate (1/1)]. ^{1}H NMR (DMSO-d_6) d 4.72 (1H, dd, H-5'$_a$), 4.88 (1H, q, H-4'), 4.93 (1H, dd, H-5'$_b$), 6.15 (2H, m, H-2' & H-3'), 6.50 (1H, d, H-1'), 7.34 - 7.65 (9H, m, m- & p-ArH), 7.90 - 8.13 (6H, m, o-ArH), 8.28 (1H, s, H-8). (This method of preparation is a modification of that described by Imai, K-i. *et al.*, Chemical and Pharmaceutical Bulletin, 1966, 14, 1377-1381, but without the use of a catalyst).

2,'3',5'-Tri-*O*-benzoyl-2-chloro-*N*-[*N*-methyl-*N*-(2-phenylethyl)- amino]adenosine

The above hydrochloride salt of 1-methyl-1-(2-phenylethyl)hydrazine (0.67 g, 1.05 mmol),

9-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.90 g, 3 mmol) and triethylamine (1.24 mL, 9 mmol) were dissolved in 1,4-dioxan (20 mL). The solution was stirred at ambient temperature for 20 h. The cooled reaction mixture was evaporated to a gum and purified by flash chromatography on silica gel. Elution with cyclohexane/ethyl acetate (4/1) initially and then with a 1/1 mixture of these solvents provided 2,'3',5'-tri-*O*-benzoyl-2-chloro-*N*-(*N*-methyl-*N*-(2-phenylethyl)amino)adenosine (1.28 g, 60%) as a foam, ^{1}H NMR (DMSO-d_6)d 2.63 (3H, s, -CH_3), 4.66 (1H, dd, H-5'$_a$), 4.77 (1H, dd, H-5'$_b$), 4.86 (1H, q, H-4'), 6.23 (1H, t, H-3'), 6.36 (1H, t, H-2'), 6.54 (1H, d, H-1'), 7.11 - 7.98 (20H, m, Ar-H), 8.44 (1H, s, H-8), 9.40 (1H, br s, N-H).

2,'3',5'-Tri-*O*-benzoyl-2-chloro-*N*-(*N*-methyl-*N*-(2-phenylethyl)amino)- adenosine (1.24 g, 1.74 mmol) was dissolved in methanolic ammonia (50 mL) and allowed to stand at ambient temperature for 20 h. The reaction mixture was evaporated and the residue was purified by flash chromatography on silica gel. Elution with dichloromethane/methanol (19/1) initially, increasing the polarity of the eluent to dichloromethane/methanol (9/1) provided the title compound (0.57 g, 78%) as semi-solid foam, TLC r_f 0.25 [SiO_2, dichloromethane/ethanol/25% aqueous ammonia solution (60/10/1)], ^{1}H NMR (DMSO-d_6) d 2.65 (3H, s, -CH_3), 3.53 - 3.60 (1H, m, H-5'$_a$), 3.63 - 3.70 (1H, m, H-5'$_a$), 4.05 (1H, q, H-4'), 4.15 (1H, q, H-3'), 4.55 (1H, q, H-2'), 5.08 (1H, t, 5'-0H), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.56 (1H, d, H-1'), 7.11 - 7.28 (5H, m, Ar-H), 8.42 (1H, s, H-8), 9.33 (1H, br s, N-H).

$C_{19}H_{23}ClN_6O_4$. 0.6 H_2O requires C, 51.2 ; H, 5.5 ; N, 18.9. Found: C, 51.3 ; H 5.4 ; N 18.7%.

EXAMPLE 2

2-Chloro-*N*-[(*N*-methyl-*N*-phenyl)amino]adenosine

The title compound was prepared according to the method described in Example 1 by reacting 1-methyl-1-phenylhydrazine (1.29 g, 11 mmol) with 9-(2',3',5'-tri-*O*-benzoyl-b-D-ribofuranosyl)-

-2,6-dichloro-9H-purine (1.58 g, 2.5 mmol) and debenzoylating the purified product using potassium carbonate in methanol to provide the title 2-Chloro-*N*-[(*N*-methyl-*N*-phenyl)amino]adenosine (0.70 g, 69%) (after column chromatography) as a colorless foam, TLC r_f 0.50 [SiO_2, THF], ^{1}H NMR (DMSO-d_6) d 3.23 (3H, 2s, CH_3), 3.50 - 3.72 (2H, br, -CH_2-), 5.06 (1H, br, 5'-OH), 5.24, 5.52 (2H, 2d, 2'- and 3'-OH), 5.86 (1H, br, H-1'), 6.70 - 6.84 (3H, m, Ar-H), 7.15 - 7.24 (2H, t, Ar-H).

$C_{17}H_{19}ClN_6O_4$. 0.66 H_2O requires C, 48.7; H, 4.9; N, 20.0. Found: C, 49.1; H 4.9; N 19.6%

EXAMPLE 3

2-Chloro-*N*-(*N*,*N*-dimethylamino)adenosine

The title compound was prepared according to the method described in Example 1 by reacting 1,1-dimethylhydrazine (0.15 g, 2.52 mmol) with 9-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)--2,6-dichloro-9H-purine (1.45 g, 2.29 mmol) and debenzoylating the purified product using methanolic ammonia to provide the title 2-chloro-*N*-(*N*,*N*-dimethylamino)adenosine (0.140 g, 29%) (after column chromatography) as a colorless foam, ^{1}H NMR (DMSO-d_6) d 2.58 (6H, s, 2 x -CH_3), 3.52 - 3.57 (1H, m, H-5'$_a$), 3.62-3.68 (1H, m, H-5'$_b$), 3.93 (1H, q, H-4'), 4.11 (1H, q, H-3'), 4.50 (1H, q, H-2'), 5.06 (1H, t, 5'-OH), 5.22, 5.48 (2H, 2d, 2'-and 3'-OH), 5.82 (1H, d, H-1'), 8.38 (1H, s, H-8), 9.34 (1H, br s, N-H).

$C_{12}H_{17}ClN_6O_4$. 0.5 EtOH. 0.5 H_20 requires C, 41.5 ; H, 5.6; N, 22.3. Found: C, 41.5; H, 5.5; N, 22.1%.

EXAMPLE 4

2-Chloro-*N*-(phenylmethoxy)adenosine.

2',3',5'-Tri-*O*-benzoyl-2-chloro-*N*-(phenylmethoxy)adenosine

This example was prepared by a method similar to that described in Example 1. 9-(2',3',5'-Tri-*O*-benzoyl–β–D-ribofuranosyl)-2,6-dichloro-9H-purine (2.0 g, 3.2 mmol), *O*-(phenylmethyl)hydroxylamine hydrochloride (0.77 g, 4.8 mmol) and *N,N*-diisopropylamine (1.03 g, 8.0 mmol) were dissolved in dioxan (50 mL). The reaction mixture was heated at reflux for 20h, filtered and evaporated in vacuo. The crude product was coevaporated with dichloromethane and crystallised from a mixture of dichloromethane and methanol to provide the title compound (1.0 g, 43%), as white crystals, mp 115 - 119°C, ^{1}H NMR ($CDCl_3$) d 3.52 - 3.70 (2H, m, H-5'$_a$ and H-5'$_b$) 3.95 (1H, d, H-4'), 4.15 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.00 (2H, s, CH_2), 5.88(1H, d, H-1'), 8.52 (1H, s, H-8).

$C_{38}H_{29}ClN_5O_8$ requires C, 63.4; H, 4.1; N, 9.7; Cl, 4.9. Found C, 63.5; H, 4.3; N, 9.5; Cl, 5.2%.

2',3',5'-Tri-*O*-benzoyl-2-chloro-*N*-(phenylmethoxy)adenosine (0.80g, 1.1 mmol) was suspended in methanolic ammonia (50 mL). The reaction mixture was stirred at room temperature for 72h. The solvent was evaporated in vacuo and the crude product was purified by flash chromatography (2 x 40cm) eluting with dichloromethane/ethanol/aqueous ammonia solution (90/10/1) to give the title 2-chloro-*N*-(phenylmethoxy)adenosine as a foam (0.40 g, 89%), ^{1}H NMR (DMSO-d_6) d 3.52 - 3.70 (2H, m, H-5'$_a$ and H-5'$_b$), 3.95 (1H, d, H-4'), 4.15 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.00 (2H, s, -CH_2-), 5.88 (1H, d, H-1'), 8.52 (1H, s, H-8). HPLC retention time 13.02 min (gradient elution over 30min; 20-80% acetonitrile/0.1% TFA in water; 99.6% purity/ 254nm).

EXAMPLE 5

N-[(4-Nitrophenyl)methoxy]adenosine

The title compound was prepared by reacting *O*-[(4-nitrophenyl)methyl]hydroxylamine hydrochloride (1.43 g, 7 mmol) with 6-chloropurine riboside (i.e. 9–β–D-ribofuranosyl-6-chloro-9H-

purine) (1.0 g, 3.5 mmol) in DMF (40 mL) at 110°C for 2 h with diisopropylethylamine (1.80 g, 14 mmol) present. The reaction mixture was evaporated and to the resultant residue was added saturated sodium bicarbonate solution (20 mL) and water (20 mL). Methanol was gradually added until the residue dissolved, and the solid which gradually precipitated was removed by filtration. The filtrate was concentrated to a residue which was purified by flash chromatography on silica gel. Elution with ethyl acetate/ ethanol (30/1) initially, followed by a (8/1) mixture of these solvents provided a solid which was recrystallised from ethanol. The first crop of material was discarded, but the second crop was confirmed as the title compound (70 mg, 7%) mp 115-117°C. TLC r_f 0.20 [SiO_2, ethyl acetate/ methanol (9/1)]; ^{1}H NMR (DMSO-d_6) d 3.46 - 3.57 (2H, m, H-5'$_a$ and H-5'$_b$), 3.90 (1H, q, H-4'), 4.08 (1H, q, H-3'), 4.43 (1H, q, H-2'), 5.07 (1H, t, 5'-OH), 5.44, 5.74 (2H, 2d, 2' and 3'-OH), 5.82 (1H, d, H-1'), 7.67 (2H, d, Ar-H), 8.08 (1h, s, H-8), 8.22 (2H, d, Ar-H), 9.34 (1H, br s, N-H).

$C_{17}H_{18}N_6O_7$. 0.75 H_2O requires C, 47.3 ; H, 4.6 ; N, 19.45. Found: C, 48.8; H, 4.55; N, 19.45%.

EXAMPLE 6

2-Chloro-*N*-(2-phenylethoxy)adenosine.

N-(2-Phenylethoxy)phthalimide

N-Hydroxyphthalimide (15.0 g, 92 mmol) and sodium acetate (7.5 g, 92 mmol) were stirred in dimethylsulfoxide (70 mL) at ambient temperature for 3h. 2-Chloroethylbenzene (12.5 g, 89 mmol) was added and the reaction mixture was heated at reflux for 2 h. After cooling and standing overnight the reaction mixture was filtered and the filtrate was poured onto ice/water (300 mL). The mixture was extracted with dichloromethane (4 x 100 mL), the combined extracts were dried ($MgSO_4$) and evaporated in vacuo to a residue. Purification by flash chromatography on a silica gel column (3 x 40 cm) eluting with heptane/ethyl acetate (1/1) afforded the title compound as a colorless foam (15.7 g, 33%); ^{1}H NMR (DMSO-d_6) d 3.05 (2H,

t, -OCH_2-), 4.39 (2H, t, -CH_2Ph), 7.20-7.35 (5H, m, Ar-H), 7.85 (4H, s, Ar-H).

O-(2-Phenylethyl)hydroxylamine hydrochloride.

N-(2-Phenylethoxy)phthalimide (11.3 g, 42 mmol) was dissolved in hot 96% ethanol (100 mL). Hydrazine hydrate (2.5 g, 50 mmol) was introduced and the reaction mixture was heated at reflux with mechanical stirring for 1.5h. The reaction mixture was stored at 4°C for 72 h, filtered and the filtrate was evaporated in vacuo. The crude white residue was suspended in toluene and stored at 4°C for 16h and filtered. The filtrate was treated with a solution of chlorotrimethyl-silane (4.34 g) in toluene (200 mL) with methanol (1.05 g) present and the title compound precipitated. The suspension was allowed to cool and the product was collected and dried in vacuo, giving a white hygroscopic solid product (5.84g, 84%). ^{1}H NMR (DMSO-d_6) d 2.95 (2H, t, -OCH_2-), 4.25 (2H, t, -CH_2Ph), 7.20 - 7.35 (5H, m, Ar-H).

2',3',5'-Tri-*O*-benzoyl-2-chloro-*N*-(2-phenylethoxy)adenosine.

9-(2',3',5'-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (2.0 g, 3.2 mmol), *O*-(2-phenylethyl)hydroxylamine hydrochloride (0.70 g, 4.0 mmol) and *N,N*-diisopropylamine (0.95 g, 7.4 mmol) were dissolved in 1,4-dioxan (40 mL) and heated at reflux for 3 days. After cooling the reaction mixture was diluted with dichloromethane (50 mL) and washed with water (2 x 30 mL). The organic phase was dried ($MgSO_4$). Flash chromatography on a silica gel column (2 x 40 cm), eluting with heptane/ethyl acetate (1/1) gave the desired product as a foam (1.54 g, 66%), ^{1}H NMR (DMSO-d_6) d 3.05 (2H, t, -OCH_2-), 4.19 (2H, t, -CH_2Ph), 4.70 (1H, dd, H-5'$_a$), 4.80 (1H, dd, H-5'$_b$), 4.90 (1H, dd, H-4'), 5.22 (1H, t, H-3'), 6.39 (1H, t, H-2'), 6.59 (1H, d, H-1'), 8.51 (1H, s, H-8).

$C_{39}H_{32}ClN_5O_8$ requires C, 63.8; H, 4.4; N, 9.5. Found C, 63.7; H, 4.5; N, 9.4%.

2',3',5,-Tri-*O*-benzoyl-2-chloro-*N*-(2-phenylethoxy)adenosine (1.54 g, 2.0 mmol) was suspended

in a solution of methanolic ammonia and stirred at room temperature for 2 days. The reaction mixture was concentrated in vacuo and the crude product was purified by flash chromatography (2 x 40 cm) eluting with dichloromethane/ethanol/aqueous ammonia solution (90/10/1), providing the product as a foam (0.48 g, 57%), ^{1}H NMR (DMSO-d_6) d 3.00 (2H, t, -CH_2O-), 3.55 - 3.70 (2H, m, H-5'$_a$ and H-5'$_b$), 3.99 (1H, d, H-4'), 4.15 - 4.20 (3H, m, -CH_2Ph and H-3'), 4.52 (1H, dd, H-2'), 5.88 (1H, d, H-1'), 8.51 (1H, s, H-8). HPLC retention time 13.64 min (gradient elution over 30min; 20-80% acetonitrile/0.1% trifluoroacetic acid in water; 99.0% purity/ 254nm).

$C_{18}H_{20}ClN_5O_5$. 0.75 H_2O requires C, 49.7; H, 5.0; N, 16.1. Found C, 49.9; H, 4.9; N, 15.8%.

EXAMPLE 7

2-Chloro-*N*-cyclopentyloxyadenosine

The title compound was prepared according to the method described in Example 6 by reacting *O*-cyclopentylhydroxylamine (prepared by the overall procedure described in example 5) (0.78 g, 5.67 mmol) with 9-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (3.0 g, 4.74 mmol), followed by debenzoylation of the purified product using methanolic ammonia to provide the title 2-chloro-*N*-cyclopentoxyadenosine (0.11 g) (after column chromatography) as a solid, mp 116-119°C. ^{1}H NMR (DMSO-d_6) d 1.50 - 1.80 (8H, m, -$CH_2CH_2CH_2CH_2$-), 3.52 - 3.58 (1H, m, H-5'$_a$), 3.63 - 3.70 (1H, m, H-5'$_b$), 3.94 (1H, q, H-4'), 4.13 (1H, q, H-3'), 4.51 (1H, q, H-2'), 4.57 (1H, br m, -OCH-), 5.06 (1H, t, 5'-0H), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 8.46 (1H, s, H-8), 11.40 (1H, s, N-H).

EXAMPLE 8

2-Chloro-*N*-methoxyadenosine.

The title compound was prepared according to the method described in Example 4 by reacting *O*-methylhydroxylamine (0.20 g, 2.0 mmol) with 9-(2',3',5'-tri-*O*-benzoyl–β–D-ribofuranosyl)--2,6-dichloro-9H-purine (1.27 g, 2.0 mmol) and debenzoylating the purified product using methanolic ammonia to provide the title 2-chloro-*N*-methoxyadenosine (0.40 g, 45%) (after column chromatography) as a colorless foam which became crystalline on trituration with dichloromethane, providing 0.20 g of a white solid, mp 123 - 125°C. ^{1}H NMR (DMSO-d_6) d 3.52 -3.59 (1H, m, H-5'$_a$), 3.63 - 3.70 (1H, m, H-5'$_b$), 3.78 (3H, s, -OCH_3), 3.96 (1H, q, H-4'), 4.14 (1H, q, H-3'), 4.52 (1H, q, H-2'), 5.06 (1H, t, 5'-0H), 5.22, 5.51 (2H, 2d, 2'-and 3'-OH), 5.87 (1H, d, H-1'), 8.50 (1H, s, H-8), 11.60 (1H, s, N-H).

$C_{11}H_{14}ClN_5O_5$. 1.33 H_2O requires C, 37.1 ; H, 4.7 ; N, 19.7. Found: C, 37.4; H, 4.4; N, 19.3%.

EXAMPLE 9

2-Chloro-*N*-ethoxyadenosine

The title compound was prepared according the method described in example 6 by reacting *O*-ethylhydroxylamine hydrochloride (0.305 g, 3.1 mmol) with 9-(2',3',5'-tri-*O*-acetyl–β–D-ribofuranosyl)-2,6-dichloro-9H-purine (1.79 g, 4.0 mmol), followed by deacylation of the purified product using sodium methoxide in methanol to provide the title 2-chloro-*N*-ethoxyadenosine (0.161 g, 21%) (after column chromatography) as a foam, ^{1}H NMR (DMSO-d_6) d 1.25 (3H, t, -$CH_2\underline{CH_3}$), 3.52 - 3.58 (1H, m, H-5'$_a$), 3.63 - 3.70 (1H, m, H-5'$_b$), 3.94 (1H, q, H-4'), 4.00 (2H, q, -$\underline{CH_2}CH_3$), 4.13 (1H, q, H-3'), 4.51 (1H, q, H-2'), 5.04 (1H, t, 5'-0H), 5.22, 5.49 (2H, 2d, 2'- and 3'-OH), 5.86 (1H, d, H-1'), 8.48 (1H, s, H-8), 11.45 (1H, s, N-H).

EXAMPLE 10

2-Chloro-*N*-(1-propyloxy)adenosine

The title compound was prepared according to the method described in Example 6 by reacting *O*-(1-propyl)hydroxylamine hydrochloride with 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)--2,6-dichloro-9H-purine, followed by deacylation of the purified product using sodium methoxide in methanol to provide the title 2-chloro-*N*-(1-propyloxy)adenosine (after column chromatography) as a foam.

EXAMPLE 11

2-Chloro-*N*-(2-methyl-1-propyloxy)adenosine

The title compound was prepared according to the method described in Example 6 by reacting isobutoxyamine hydrochloride (0.603 g, 4.8 mmol) with 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.79 g, 4.0 mmol), followed by deacylation of the purified product using sodium methoxide in methanol to provide the title 2-chloro-*N*-ethoxyadenosine (0.31 g, 42%) (after column chromatography) as a foam, ^{1}H NMR (DMSO-d_6) d 0.96 (6H, 2t, -$CH(CH_3)_2$), 2.0 (1H, h, -$CH_2CH(CH_3)_2$), 3.52 - 3.58 (1H, m, H-5'$_a$), 3.63 - 3.70 (1H, m, H-5'$_b$), 3.73 (2H, d, -$CH_2CH(CH_3)_2$), 3.95 (1H, q, H-4'), 4.14 (1H, q, H-3'), 4.50 (1H, q, H-2'), 5.04 (1H, t, 5'-0H), 5.20, 5.48 (2H, 2d, 2'- and 3'-OH), 5.85 (1H, d, H-1'), 8.47 (1H, s, H-8), 11.48 (1H, s, N-H).

EXAMPLE 12

2-Chloro-*N*-(3-propenyloxy)adenosine

The title compound was prepared according to the method described in Example 6 by reacting

O-allylhydroxylamine hydrochloride (0.526 g, 4.8 mmol) with 9-(2',3',5'-tri-*O*-acetyl–β–D-ribofuranosyl)-2,6-dichloro-9H-purine (1.79 g, 4.0 mmol), followed by deacylation of the purified product using sodium methoxide in methanol to provide the title 2-chloro-*N*-ethoxyadenosine (0.39 g, 60%) (after column chromatography) as a foam, ^{1}H NMR (DMSO-d_6) d 3.53 - 3.59 (1H, m, H-5'$_a$), 3.62 - 3.69 (1H, m, H-5'$_b$), 3.95 (1H, q, H-4'), 4.04 (1H, q, H-3'), 4.48 (2H, d, -C$\underline{H}_2$CH=CH$_2$), 4.51 (1H, q, H-2'), 5.06 (1H, t, 5'-OH), 5.22, 5.48 (2H, 2d, 2'- and 3'-OH), 5.26 (1H, dd, -CH$_2$CH=C$\underline{H}$), 5.37 (1H, dd, -CH$_2$CH=C$\underline{H}$), 5.85 (1H, d, H-1'), 6.04 (1H, qt, -CH$_2$C$\underline{H}$=CH$_2$), 8.48 (1H, s, H-8), 11.50 (1H, s, N-H).

EXAMPLE 13

2-Chloro-*N*-(1,1-dimethylethoxy)adenosine

The title compound was prepared according to the method described in Example 6 by reacting O-tert-butylhydroxylamine hydrochloride (0.603 g, 4.8 mmol) with 9-(2',3',5'-tri-*O*-acetyl–β–D–ribofuranosyl)-2,6-dichloro-9H-purine (1.79 g, 4.0 mmol), followed by deacylation of the purified product using sodium methoxide in methanol to provide the title 2-chloro-*N*-ethoxyadenosine (0.296 g, 56%) (after column chromatography) as a foam, ^{1}H NMR (DMSO-d_6) d .1.27 (9H, m, -C(C$\underline{H}_3$)$_3$), 3.52 - 3.58 (1H, m, H-5'$_a$), 3.62 - 3.69 (1H, m, H-5'$_b$), 3.94 (1H, q, H-4'), 4.14 (1H, q, H-3'), 4.52 (1H, q, H-2'), 5.05 (1H, t, 5'-OH), 5.22, 5.50 (2H, 2d, 2'- and 3'-OH), 5.85 (1H, d, H-1'), 8.47 (1H, s, H-8), 11.01 (1H, s, N-H).

EXAMPLE 14

2-Chloro-*N*-[2-(phenoxy)ethoxy]adenosine

The title compound was prepared by reacting *O*-[2-(phenoxy)ethyl]hydroxylamine (prepared by the procedure described in Example 6) (0.94 g, 5.0 mmol) with 9-(2',3',5'-tri-*O*-benzoyl–β–D–

ribofuranosyl)-2,6-dichloro-9H-purine (2.0 g, 3.16 mmol), followed by debenzoylation of the purified product using methanolic ammonia to provide the title 2-chloro-*N*-[2-(phenoxy)ethoxy]adenosine (0.44 g, 32%) (after column chromatography) as a colorless foam, ^{1}H NMR (DMSO-d_6) d 3.52 - 3.59 (1H, m, H-5'$_a$), 3.63 - 3.70 (1H, m, H-5'$_b$), 3.94 (1H, q, H-4'), 4.11 (1H, q, H-3'), 4.32 (4H, dt, -OCH_2CH_2O-), 4.50 (1H, q, H-2'), 5.06 (1H, t, 5'-0H), 5.22, 5.50 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 6.92 - 6.97 (3H, m, Ar-H), 7.26 - 7.33 (2H, dd, Ar-H), 8.51 (1H, s, H-8), 11.64 (1H, br, N-H).

$C_{18}H_{20}ClN_5O_4$. 0.66 H_20 requires C, 48.1 ; H, 4.8 ; N, 15.6. Found: C, 48.1; H, 4.7; N, 15.4%.

EXAMPLE 15

2-Chloro-*N*-(1,2,3,4-tetrahydronaphth-1-yloxy)adenosine.

The title compound was prepared according to the method described in Examples 4 and 5 by reacting *O*-[1,2,3,4-tetrahydronaphth-1-yl)hydroxylamine (prepared by the procedure described in example 6) (0.35 g, 2.0 mmol) with 9-(2',3',5'-tri-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloro--9H-purine (1.0 g, 1.58 mmol) and debenzoylating the purified product using methanolic ammonia to provide the title 2-chloro-*N*-(1,2,3,4-tetrahydronaphth-1-yloxy)adenosine (0.10 g, 15%) (after column chromatography) as a colorless foam (a mixture of diastereoisomers), ^{1}H NMR (DMSO-d_6) d 1.65 - 2.85 (6H, m, -$CH_2CH_2CH_2$-), 3.53 -3.61 (1H, m, H-5'$_a$), 3.64 - 3.70 (1H, m, H-5'$_b$), 3.94 (1H, br d, H-4'), 4.16 (1H, br d, H-3'), 4.53 (1H, q, H-2'), 5.07 (2H, m, 5'-0H and -OCH-), 5.26, 5.53 (2H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 7.13 - 7.30 (3H, m, Ar-H), 7.88 - 7.96 (1H, m, Ar-H), 8.52 (1H, s, H-8), 11.60 (1H, br s, N-H). HPLC retention time 20.71 and 20.95 min (gradient elution over 25 min.; 25-45% acetonitrile/ 0.1M.

EXAMPLE 16

2,*N*-Dimethoxyadenosine.

2-Chloro-*N*-methoxyadenosine (Example 8) (0.20 g, 0.60 mmol) was added to a mixture of sodium hydride (40 % oil dispersion) (0.12 g, 3.0 mmol) methanol (0.24 mL) and DMF (5 mL) which had been stirred under nitrogen at room temperature for 1 h. The reaction mixture was heated at 80°C for 16 h, cooled and evaporated. Flash chromatography provided the title 2,*N*-dimethoxyadenosine, still however containing some starting 2-chloro-*N*-methoxyadenosine. ^{1}H NMR (DMSO-d_6)d 3.52 -3.59 (1H, m, H-5'$_a$), 3.63 - 3.70 (1H, m, H-5'$_b$), 3.77 (3H, s, -OCH_3), 3.97 (1H, q, H-4'), 4.14 (1H, q, H-3'), 4.60 (1H, q, H-2'), 5.09 (1H, t, 5'-0H), 5.18, 5.44 (2H, 2d, 2'-and 3'-OH), 5.83 (1H, d, H-1'), 8.24 (1H, s, H-8), 11.04 (1H, s, N-H) (desired product only quoted).

EXAMPLE 17

2-Methylthio-*N*-[2-(phenoxy)ethoxy]adenosine.

9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-6-chloro-2-methylthio-9H-purine (0.50 g, 1.1 mmol) (prepared using the procedure described in US 5,432,164), *O*-[2-(phenoxy)ethoxy]hydroxylamine hydrochloride (0.41 g, 2.16 mmol) (see Example 9) and triethylamine (0.45 g, 4.4 mmol) were stirred at 100°C in dioxan (20 mL) for 6 h, and at ca. 95°C for 65 h. The product, after column chromatography, was deprotected using methanolic ammonia, to provide the title 2-methylthio-*N*-[2-(phenoxy)ethoxy]adenosine (0.09 g, 18%), (after column chromatography) as a colorless foam, [tlc R_f 0.26 (SiO_2, dichloromethane/methanol (9/1)], ^{1}H NMR (DMSO-d_6) d 2.51 (3H, s, -SCH_3), 3.52 - 3.60 (1H, m, H-5'a), 3.62 - 3.69 (1H, m, H-5'$_b$), 3.94 (1H, q, H-4'), 4.16 (1H, q, H-3'), 4.30 (4H, br d, -OCH_2CH_2O-), 4.61 (1H, q, H-2'), 5.04 (1H, t, 5'-0H), 5.23, 5.50 (2H, 2d, 2'-and 3'-OH), 5.90 (1H, d, H-1'), 6.92 - 7.01 (3H, m, Ar-H), 7.32 (2H, dd, Ar-H), 8.36 (1H, s, H-8), 11.20 (1H, s, N-H).

EXAMPLE 18

2-Amino-*N*-(dimethylamino)adenosine.

The title compound was prepared according to the method described in Example 4 by reacting 1,1-dimethylhydrazine (0.79 g, 13.1 mmol) with 9-(2,3,5-tri-*O*-acetyl–β–D-ribofuranosyl)-2-amino-6-chloro-9H-purine (4.0 g, 9.35 mmol) and debenzoylating the purified product using methanolic ammonia to provide the title 2-amino-*N*-(dimethylamino)adenosine (after column chromatography) as an amorphous foam (0.56 g, 45%), ^{1}H NMR (DMSO-d_6) d 2.54 (6H, s, 2 x $-CH_3$), 3.50 - 3.57 (1H, m, H-5'$_a$), 3.61 - 3.68 (1H, m, H-5'$_b$), 3.93 (1H, q, H-4'), 4.12 (1H, q, H-3'), 4.51 (1H, q, H-2'), 5.12, 5.38 (2H, 2d, 2'-and 3'-OH), 5.42 (1H, t, 5'-OH), 5.76 (1H, d, H-1'), 5.95 (2H, s, $-NH_2$), 7.93 (1H, s, H-8), 8.20 (1H, s, N-H).

EXAMPLE 19

2-Chloro-*N*-[*N*-methyl-*N*-(2-phenoxyethyl)amino]adenosine

The title compound was prepared by reacting 1-methyl-1-(2-phenoxyethyl)hydrazine (prepared by the general method described in Example 1) (0.80 g, 4 mmol) and 9-(2,3,5-tri-*O*-benzoyl–β–D-ribofuranosyl)-2,6dichloro-9H-purine (2.53 g, 4 mmol) and triethylamine (1.11 mL, 8 mmol) in dioxan (25 mL), followed by debenzoylation of the purified product using methanolic ammonia to provide the title 2-chloro-*N*-(*N*-methyl-*N*-(2-phenoxyethyl)amino)adenosine (0.84 g, 47%) (after column chromatography) obtained as a solid, mp 166-8°C, ^{1}H NMR (DMSO-d_6) d 2.70 (3H, s, $-CH_3$), 3.22 (2H, br t, $-CH_2-$), 3.51 - 3.58 (1H, m, H-5'$_a$), 3.62 - 3.69 (1H, m, H-5'$_a$), 3.95 (1H, q, H-4'), 4.05 - 4.15 (3H, m, $-CH_2-$ and H-3'), 4.50 (1H, q, H-2'), 5.06 (1H, t, 5'-OH), 5.21, 5.49 (2H, 2d, 2'-and 3'-OH), 5.81 (1H, d, H-1'), 6.79 - 7.25 (5H, m, Ar-H), 8.41 (1H, s, H-8), 9.41 (1H, br s, N-H).

EXAMPLE 20

N-Cyclopentoxy-2-methyladenosine

O-Cyclopentylhydroxylamine hydrochloride (0.52 g, 3.75 mmol) was reacted with 9-(2',3',5'-tri-*O*-acetyl–β–D-ribofuranosyl)-6-chloro-2-methyl-9H-purine (1.07 g, 2.5 mmol) [prepared from 2-methylinosine (Journal of Organic Chemistry, 1967, *32*, 3258 - 3260) by standard acylation and chlorination steps] in dioxan (40 mL) in the presence of triethylamine (0.63 g, 6.25 mmol). The reaction mixture was heated at 100°C in a sealed vessel for 70h, before being filtered and evaporated. The product (after purification by chromatography) was debenzoylated using methanolic ammonia to provide the title *N*-cyclopentoxy-2-methyladenosine (after column chromatography) as a foam, ^{1}H NMR (DMSO-d_6) d 1.47 - 1.93 (8H, m, -$CH_2CH_2CH_2CH_2$-), 2.32 (3H, s, -CH_3), 4.59 (1H, br m, -O-CH-), 5.88 (1H, d, H-1').

EXAMPLE 21

N-Methoxy-2-methyladenosine

O-Methylhydroxylamine hydrochloride (0.20 g, 2.4 mmol) was reacted with 9-(2',3',5'-tri-*O*-acetyl–β–D-ribofuranosyl)-6-chloro-2-methyl-9H-purine (0.85 g, 2.0 mmol) (see Example 20) in dioxan (40 mL) in the presence of triethylamine (0.52 g, 5.0 mmol). The reaction mixture was heated at 90°C in a sealed vessel for 70h, before being filtered and evaporated. The product (after purification by chromatography) was debenzoylated using methanolic ammonia to provide the title compound (after column chromatography) as a foam, ^{1}H NMR (DMSO-d_6) d 2.30 (3H, s, 2-CH_3), 3.48 - 3.55 (1H, m, H-5'$_a$), 3.60 - 3.67 (1H, m, H-5'$_b$), 3.77 (3H, s, -OCH_3), 3.92 (1H, q, H-4'), 4.08 (1H, q, H-3'), 4.45 (1H, q, H-2'), 5.22 (1H, dt, 5'-0H), 5.17, 5.40 (2H, 2d, 2'- and 3'-OH), 5.71 (1H, d, H-1'), 7.99 (1H, s, H-8), 10.85 (1H, s, N-H).

EXAMPLE 22

N-methoxy-2-phenyladenosine

O-Methylhydroxylamine hydrochloride (10.2 g, 12.2 mmol) was reacted with 9-(2',3',5'-tri-*O*-acetyl–β–D-ribofuranosyl)-6-chloro-2-phenyl-9H-purine (0.60 g, 1.2 mmol) in dioxan (30 mL) in the presence of diisopropylethylamine (1.70 g, 13.1 mmol). The reaction mixture was heated at 100°C in a sealed vessel for 18h, and at 60°C for 50h before being filtered and evaporated. The product (after purification by chromatography) was debenzoylated using methanolic ammonia to provide the title *N*-methoxy-2-phenyladenosine (0.085 g, 19%) (after column chromatography) as a foam, ^{1}H NMR (DMSO-d_6) d 3.55 - 3.62 (1H, m, H-5'$_a$), 3.66 - 3.73 (1H, m, H-5'$_b$), 3.87 (3H, s, -OCH_3) 3.97 (1H, q, H-4'), 4.23 (1H, q, H-3'), 4.72 (1H, q, H-2'), 5.02 (1H, dt, 5'-0H), 5.26, 5.52 (2H, 2d, 2'- and 3'-OH), 6.05 (1H, d, H-1'), 7.44 - 7.52 (3H, m, Ar-H), 8.38 (2H, dd Ar-H), 8.49 (1H, s, H-8), 11.04 (1H, s, N-H).

EXAMPLE 23

5'-Deoxy-2,5'-dichloro-*N*-(1-piperidinyl)adenosine

5'-Deoxy-2,5'-dichloro-2',3'-*O*-1-methylethylidene)-*N*-(1-piperidinyl)- adenosine

2-Chloro-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine [prepared by protection of 2-Chloro-*N*-(1-piperidinyl)adenosine (Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666)] (0.28 g, 0.47 mmol), triphenylphosphine (0.31 g, 1.18 mmol) and tetrachloromethane (0.18 g, 1.18 mmol) was stirred in dry dimethylformamide (10 mL) at 20°C for 48 h. The reaction mixture was concentrated in vacuo and the crude product was purified by flash chromatography eluting with dichloromethane and 10% ammonia in ethanol (95:5) to give 5'-deoxy-2,5'-dichloro-2',3'-*O*-(1-methyl-ethylidene)-*N*-(1-piperidinyl)adenosine (0.10 g, 48%) as a foam. ^{1}H-NMR (400 MHz, DMSO-d_6)

d 1.34 (3H, s, -CH_3), 1.36 (2H, m, piperidine C-H), 1.62 (4H, m, piperidine C-H), 2.82 (4H, br, piperidine C-H), 3.78, 3.88 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.35 (1H, ddd, H-4'), 5.02 (1H, dd, H-3'), 5.39 (1H, dd, H-2'), 6.20 (1H, d, H-1'), 8.36 (1H, s, H-8). HPLC retention time 21.45 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

Deprotection of 5'-deoxy-2,5'-dichloro-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine (0.11 g, 0.25 mmol) was performed by dissolving the compound in a mixture of ethanol (5 mL) and sulfuric acid (0.2M, 5 mL) and stirring the mixture for 72 h. at room temperature. The reaction mixture was neutralized with aqueous sodium bicarbonate and extracted with dichloromethane (3 x 50 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The product was purified by flash chromatography on silica gel, eluting with a mixture of dichloromethane and 10% ammonia solution in ethanol (9:1), to provide the title 5'deoxy-2,5'-dichloro-*N*-(1-piperidinyl)adenosine (0.1 g, 99%) as a foam, ^{1}H-NMR (400 MHz, DMSO-d_6) d 1.35 (2H, br, piperidine C-H), 1.62 (4H, br, piperidine C-H), 2.80 (4H, br, piperidine C-H), 3.82, 3.93 (1H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, dd, H-4'), 4.18 (1H, dd, H-3'), 4.63 (1H, dd, H-2'), 5.88 (1H, d, H-1'), 8.39 (1H, s, H-8). HPLC retention time 10.95 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 99% purity at 250 nm).

EXAMPLE 24

(S)-5'-Deoxy-2,5'-dichloro-*N*-[2-(methylmethoxy)-1-pyrrolidinyl]adenosine

(S)-2-Chloro-*N*-[2-(methylmethoxy)-1-pyrrolidinyl]adenosine [WO 93/08206 (Novo Nordisk A/S), Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666] (0.35 g, 0.8 mmol) was dissolved in acetonitrile (5 mL) and cooled on an ice-water bath. Under a nitrogen atmosphere, thionyl chloride (0.34 g, 0.2 mL, 2.4 mmol) (see Borchardt, R.T., Huber, J.A. and Wu, Y.S., Journal of Organic Chemistry, **1976**, *41*, 565-567) was added and a precipitate appeared which dissolved over the following 15 min. Pyridine (0.13 mL, 0.13 g, 1.6 mmol) was introduced gradually, the reaction mixture became

yellow in colour and was allowed to reach room temperature gradually. After stirring the mixture overnight, ice was added and the reaction mixture was neutralised to pH 7 with aqueous sodium bicarbonate prior to extraction with ethyl acetate (2 x 10 mL). The combined extracts were dried ($MgSO_4$) and evaporated to provide the intermediate 2,3-*O*-sulphinyl derivative (0.35 g), to which was added methanol (5 mL), water (1 mL) and 25% aqueous ammonia solution (0.25 mL) and this mixture was stirred for 16 h. The solution was evaporated in vacuo, and the resultant residue was purified by flash chromatography on silica gel eluting with a mixture of dichloromethane and 10% ammonia in ethanol (17:3), to provide the title (S)-5'-deoxy-2,5'-dichloro-*N*-[2-(methylmethoxy)-1-pyrrolidinyl]adenosine (0.12 g, 34%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.50 - 1.60 (1H, br, pyrrolidine C-H), 1.78 (2H, br q, pyrrolidine C-H), 1.92 - 2.03 (1H, br, pyrrolidine C-H), 3.85, 3.95 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.09 (1H, br dd, H-4'), 4.17 (1H, dd, H-3'), 4.67 (1H, dd, H-2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 8.38 (1H, s, H-8), 9.34 (1H, br s, -NH). HPLC retention time 9.65 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 99% purity at 250 nm).

$C_{16}H_{22}Cl_2N_6O_4$. 0.25 H_2O requires C, 43.9; H, 5.2; N, 19.2. Found: C, 43.7; H, 5.4; N, 19.4%.

EXAMPLE 25

5'-Deoxy-2,5'-dichloro-*N*-(4-phenoxy-1-piperidinyl)adenosine

This compound was prepared by the general method described in Example 24. 2-Chloro-*N*-(4-phenoxy-1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (0.5 g, 1.05 mmol) was subjected to the chlorination conditions described above (Example 24), providing the title 5'-deoxy-2,5'-dichloro-*N*-(4-phenoxy-1-piperidinyl)adenosine which precipitated on treatment with dichloromethane following trituration with ether. Drying in vacuo provided a solid (0.28 g, 56%), m.p. 165-170°C, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.74 - 1.84 (2H, br, piperidine C-H), 1.99 - 2.08 (2H, br, piperidine C-H), 2.80 - 2.90 (2H, br, piperidine C-H), 3.04 - 3.12 (2H, br, piperidine C-H), 3.85, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.09 (1H, q,

H-4'), 4.18 (1H, q, H-3'), 4.44 (1H, br, PhO-C-H) 4.66 (1H, dd, H-2'), 5.50, 5.63 (2H, 2d, 2'- and 3'-OH), 5.89 (1H, d, H-1'), 6.94 (1H, t, Ar-H), 6.99 (2H, d, Ar-H), 7.30 (2H, t, Ar-H), 8.40 (1H, s, H-8). HPLC retention time 19.15 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 99.9% purity at 250 nm).

EXAMPLE 26

5'-Deoxy-2,5'-dichloro-*N*-(3-methoxy-1-piperidinyl)adenosine

This compound was prepared by the general method described in Example 24. 2-Chloro-*N*--(3-methoxy-1-piperidinyl)adenosine (prepared by *O*-methylation of *N*-tertbutyloxycarbonyl-3-hydroxypiperidine, followed by use of the *N*-amination technique described in Overberger, C.G. and Herin, L.P. Journal of Organic Chemistry, **1962**, *27*, 417, and further reaction of the resultant hydrazine as described in Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666) (0.1 g, 0.24 mmol) was subjected to the chlorination conditions described in Example 24, providing the title 5'-deoxy-2,5'-dichloro-*N*-(3-methoxy-1-piperidinyl)adenosine (mixture of diastereoisomers) (0.07 g, 67%), following column chromatography, as a solid, m.p. 200 - 202°C. ^{1}H-NMR (400MHz, DMSO-d_6) d 3.86, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.11 (1H, q, H-4'), 4.19 (1H, q, H-3'), 4.65 (1H, dd, H--2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.88 (1H, d, H-1'), 8.39 (1H, s, H-8). HPLC retention time 17.08 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 98.7% purity at 250 nm).

EXAMPLE 27

5'-Deoxy-2,5'-dichloro-*N*-(4-phenylthio-1-piperidinyl)adenosine

This compound was prepared by the method described in Example 24. 2-Chloro-*N*-(4-phenylthio-1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (5.49 g,

11.1 mmol) was subjected to the reaction conditions described above (Example 24), providing the title 5'-deoxy-2,5'-dichloro-*N*-(4-phenylthio-1-piperidinyl)adenosine which precipitated from the aqueous methanolic ammonia. Recrystallization provided a solid (3.93 g, 69%), m.p. 154 - 157°C, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.74 - 1.84 (2H, br, piperidine C-H), 1.95 - 2.05 (2H, br, piperidine C-H), 2.80 - 2.90 (1H, br, piperidine C-H), 3.04 - 3.12 (2H, br, piperidine C-H), 3.84, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.17 (1H, q, H-3'), 4.64 (1H, dd, H-2'), 5.48, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 7.26 (1H, t, Ar-H), 7.35 (2H, t, Ar-H), 7.42 (2H, d, Ar-H), 8.38 (1H, s, H-8), 9.49 (1H, s, N-H). HPLC retention time 22.19 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 100% purity at 250 nm).

EXAMPLE 28

5'-Deoxy-2,5'-dichloro-*N*-(3-phenylthio-1-piperidinyl)adenosine

This compound was prepared by the method described in Example 24. 2-Chloro-*N*-(4-phenylthio-1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (0.5 g, 1 mmol) was subjected to the reaction conditions described above, providing the title 5'-deoxy-2,5'-dichloro-*N*-(3-phenylthio-1-piperidinyl)adenosine (mixture of diastereoisomers) as a foam (0.48 g, 94%) following flash chromatography on silica gel. ^{1}H-NMR (400MHz, DMSO-d_6) d 3.84, 3.92 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.17 (1H, q, H-3'), 4.64 (1H, dd, H-2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 7.22 (1H, t, Ar-H), 7.31 (2H, t, Ar-H), 7.43 (2H, d, Ar-H), 8.39 (1H, s, H-8). HPLC retention time 17.08 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 98.7% purity at 250 nm).

EXAMPLE 29

5'-Deoxy-2,5'-dichloro-*N*-(4-phenylsulfinyl-1-piperidinyl)adenosine

2',3'-Di-*O*-acetyl-5'-deoxy-2,5'-dichloro-*N*-(4-phenylthio-1-piperidinyl)adenosine (prepared by

acetylation of Example 5) (2.95 g, 5 mmol) was dissolved in dry dichloromethane (100 mL). "Oxone" (7.7 g, 2.5 equiv.) and wet clay (Hirano, M., Tomaru, J. and Morimoto, T. Bull. Chem. Soc. Japan, 1991, *64*, 3752-3754) (5.95 g) were introduced with vigorous stirring. Both the phenylsulphinyl product (R_f = 0.21) and the phenylsulphonyl product (R_f = 0.45) were apparent by TLC [SiO_2, ethyl acetate/methanol (9:1)] and after 0.5 h. reaction time the reaction mixture was filtered. The filtrate was washed with water (2 x 100 mL), dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of ethyl acetate and heptane (1:1), then with ethyl acetate, and finally with a mixture of ethyl acetate and methanol (19:1), to provide 2',3'-di-*O*-acetyl-5'-deoxy-2,5'-dichloro-*N*-(4-phenylsulfinyl-1-piperidinyl)adenosine (0.18 g, 6%) and 2',3'-di-*O*-acetyl-5'-deoxy-2,5'-dichloro-*N*-(4-phenylsulphonyl-1-piperidinyl)adenosine (1.2 g, 39 %) as foams.

5'-Deoxy-2,5'-dichloro-*N*-(4-phenylsulfinyl-1-piperidinyl)adenosine

2',3-Di-*O*-acetyl-5'-deoxy-2,5'-dichloro-*N*-(4-phenylsulfinyl-1-piperidinyl)adenosine (0.22 g, 0.36 mmol) was dissolved in methanol (10 mL) and methanolic ammonia (1 mL) was introduced. After 1 h. at room temperature, the reaction mixture was evaporated to a residue and purified by flash chromatography on silica gel, eluting with a mixture of dichloromethane and ethanol (9:1) to provide 5'-deoxy-2,5'-dichloro-*N*-(4-phenylsulfinyl-1-piperidinyl)adenosine (0.1 g, 53%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) d 3.84, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.17 (1H, q, H-3'), 4.63 (1H, dd, H-2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 7.53 - 7.66 (5H, m, Ar-H), 8.38 (1H, s, H-8). HPLC retention time 14.24 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 95.4% purity at 250 nm).

EXAMPLE 30

5'-Deoxy-2,5'-dichloro-*N*-(4-phenylsulfonyl-1-piperidinyl)adenosine

2',3-Di-*O*-acetyl-5'-deoxy-2,5'-dichloro-*N*-(4-phenylsulfonyl-1-piperidinyl) adenosine (generated

during the preparation of Example 29) (1.2 g, 1.9 mmol) was dissolved in methanol (90 mL) and methanolic ammonia (10 mL) was introduced. After 0.5 h. at room temperature, the reaction mixture was evaporated to a residue and purified by flash chromatography on silica gel, eluting with a mixture of dichloromethane and ethanol (9:1) to provide 5'-deoxy-2,5'-dichloro-*N*-(4-phenylsulphonyl-1-piperidinyl)adenosine (0.82 g, 79%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) d 3.84, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.09 (1H, dt, H-4'), 4.16 (1H, ps t, H-3'), 4.62 (1H, dd, H-2'), 5.49, 5.62 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 7.71 (2H, t, Ar-H), 7.80 (1H, t, Ar-H), 7.90 (1H, d, Ar-H), 8.39 (1H, s, H-8). HPLC retention time 13.78 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96.9% purity at 250 nm).

EXAMPLE 31

5'-Deoxy-2,5'-dichloro-*N*-(4-phenyl-1-piperidinyl)adenosine

2-Chloro-*N*-(4-phenyl-1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (0.3 g, 0.65 mmol) was subjected to the chlorination conditions described in Example 24, providing the title 5'-deoxy-2,5'-dichloro-*N*-(4-phenyl-1-piperidinyl)adenosine as a foam (0.28 g, 90%), ^{1}H-NMR (400MHz, DMSO-d_6) d 3.86, 3.95 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.11 (1H, q, H-4'), 4.21 (1H, q, H-3'), 4.66 (1H, dd, H-2'), 5.49, 5.63 (2H, 2d, 2'- and 3'-OH), 5.89 (1H, d, H-1'), 7.20 (1H, dt, Ph-C-H), 7.31 (5H, d, Ar-H), 8.40 (1H, s, H-8), 9.45 (1H, s, N-H). HPLC retention time 20.92 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 99.75% purity at 250 nm).

EXAMPLE 32

5'-Deoxy-2,5'-dichloro-*N*-(1-morpholinyl)adenosine

This compound was prepared by the method described in Example 23. 2-Chloro-*N*-(1-morpholinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (1.0 g, 2.6 mmol) was subjected

to the chlorination conditions described in Example 24, providing the title 5'-deoxy-2,5'-dichloro-*N*-(1-morpholinyl)adenosine as a foam (0.78 g, 74%), ^{1}H-NMR (400MHz, DMSO-d_6) d 2.38 (4H, br, morpholine C-H), 3.71 (4H, br, morpholine C-H), 3.85, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.18 (1H, q, H-3'), 4.64 (1H, q, H-2'), 5.50, 5.63 (1H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 8.41 (1H, s, H-8), 9.50 (1H, s, NH). HPLC retention time 7.82 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 97.8% purity at 250 nm).

$C_{14}H_{18}Cl_2N_6O_4$.0.5 EtOH requires C, 42.1; H, 4.9; N, 19.6. Found: C, 41.6; H, 5.2; N, 19.0%.

EXAMPLE 33

5'-Deoxy-2,5'-dichloro-*N*-(dimethylamino)adenosine

This compound was prepared by the method described in Example 24. 2-Chloro-*N*-(dimethylamino)adenosine [WO 93/23417 (Novo Nordisk A/S)] (0.62 g, 1.8 mmol) was subjected to the chlorination conditions described above (Example 24), providing the title 5'-deoxy-2,5'-dichloro-*N*-(dimethylamino)adenosine as a solid (0.23 g, 41%) after column chromatography, m.p. 188-189°C, ^{1}H-NMR (400MHz, DMSO-d_6) d 2.59 (6H, s, $N(CH_3)_2$), 3.85, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.18 (1H, q, H-3'), 4.66 (1H, q, H-2'), 5.50, 5.62 (1H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 8.38 (1H, s, H-8), 9.39 (1H, br, NH).

$C_{12}H_{16}Cl_2N_6O_3$.0.25 H_2O. 0.25 EtOH requires C, 39.6; H, 4.8; N, 22.2. Found: C, 39.5; H, 4.5; N, 22.3%.

EXAMPLE 34

5'-Deoxy-2,5'-dichloro-*N*-methoxyadenosine

This compound was prepared by the method described in Example 24. 2-Chloro-*N*--(methoxy)adenosine [WO 93/23417 (Novo Nordisk A/S)] (0.8 g, 2.4 mmol) was subjected to the chlorination conditions described above (Example 24), providing the title 5'-deoxy-2,5'-dichloro-*N*-methoxyadenosine as a foam (0.34 g, 40%), ^{1}H-NMR (400MHz, DMSO-d_6) d 3.78 (3H, s, -OCH_3), 3.85, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, q, H-4'), 4.19 (1H, q, H-3'), 4.66 (1H, q, H-2'), 5.51, 5.65 (1H, 2d, 2'-and 3'-OH), 5.90 (1H, d, H-1'), 8.45 (1H, s, H-8), 11.59 (1H, s, NH). HPLC retention time 6.99 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96.5% purity at 250 nm).

EXAMPLE 35

N-Cyclopentoxy-5'-deoxy-2,5'-dichloroadenosine

This compound was prepared by the method described in more detail in Example 23. *N*-Cyclopentoxy-2-chloroadenosine [WO 93/23417 (Novo Nordisk A/S)] (1.0 g, 2.6 mmol) was subjected to the chlorination conditions described in Example 24, providing the title *N*-cyclopentoxy-5'-deoxy-2,5'-dichloroadenosine as a foam (0.82 g, 78%), ^{1}H-NMR (400MHz, DMSO-d_6) d 1.49 - 1.92 (8H, 3m, cyclopentyl C-H), 3.86, 3.94 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.11 (1H, q, H-4'), 4.20 (1H, q, H-3'), 4.59 (1H, m, -OC-H), 4.67 (1H, q, H-2'), 5.51, 5.64 (1H, 2d, 2'-and 3'-OH), 5.90 (1H, d, H-1'), 8.44 (1H, s, H-8), 11.44 (1H, s, NH). HPLC retention time 12.2 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 97.4% purity at 250 nm).

$C_{15}H_{19}Cl_2N_5O_4$.0.5 EtOH requires C, 45.0; H, 5.2; N, 16.4. Found: C, 45.2; H, 5.1; N, 16.2%.

EXAMPLE 36

2-Bromo-5'-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

This compound was prepared by the method described in Example 23. 2-Bromo-*N*--(1-piperidinyl)adenosine [WO 93/23417 (Novo Nordisk A/S)] (0.06 g, 0.14 mmol) was subjected to the chlorination conditions described in Example 24, providing the title 2-bromo-5'-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine as a foam (0.016 g, 26%), ^{1}H-NMR (400MHz, DMSO-d_6) d 1.37 (2H, br, piperidine C-H), 1.64 (4H, br, piperidine C-H), 2.80 (4H, br, piperidine C-H), 3.85, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.09 (1H, q, H-4'), 4.18 (1H, q, H-3'), 4.65 (1H, q, H-2'), 5.48, 5.62 (1H, 2d, 2'-and 3'-OH), 5.87 (1H, d, H-1'), 8.33 (1H, s, H-8), 9.36 (1H, s, NH). HPLC retention time 9.65 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 94% purity at 250 nm).

EXAMPLE 37

2-Amino-5'-chloro-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine

This compound was prepared by the method described in Example 24. 2-Amino-*N*--(4-phenylthio-1-piperidinyl)adenosine [prepared by reaction of 9-(2',3',5'-tri-*O*-acetyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666) with 1-amino-4-phenylthiopiperidine] (0.47 g, 1.0 mmol) was subjected to the chlorination conditions described above (Example 24). Column chromatography on silica gel, eluting initially with a mixture of heptane and ethyl acetate (7:3), increasing polarity to pure ethyl acetate provided the title 2-amino-5'-chloro-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine (0.1 g, 20%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) d 1.65 (2H, dq, piperidine C-H), 1.91 - 2.01 (2H, br, piperidine C-H), 2.75 (2H, br t, piperidine C-H), 2.98 - 3.07 (2H, br, piperidine C-H), 3.82, 3.92 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.04 (1H, dt, H-4'), 4.15 (1H, q, H-3'), 4.64 (1H, dd, H-2'), 5.36, 5.52 (2H, 2d, 2'- and 3'-OH), 5.77 (1H, d, H-1'), 5.96 (1H, br s, -NH_2), 7.27 (1H, t, Ar-H), 7.37 (2H, t, Ar-H), 7.42 (2H, d, Ar-H), 7.91, 8.18 (2H, 2s, H-8, N-H).

EXAMPLE 38

5'-Chloro-5'-deoxy-2-methylthio-*N*-(1-piperidinyl)adenosine

2-Methylthio-*N*-(1-piperidinyl)adenosine [WO 93/23417 (Novo Nordisk A/S)] (0.15 g, 0.38 mmol) was subjected to the chlorination conditions described in Example 24, providing 5'-chloro-5'-deoxy-2-methylthio-*N*-(1-piperidinyl)adenosine as a solid (0.07 g, 45%) mp 213 - 215°C. ^{1}H-NMR (400MHz, DMSO-d_6) d 1.37 (2H, br, piperidine C-H), 1.62 (4H, br q, piperidine C-H), 2.48 (3H, s, -SCH_3), 2.81 (4H, br, piperidine C-H), 3.83, 3.93 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.08 (1H, q, H-4'), 4.23 (1H, q, H-3'), 4.75 (1H, q, H-2'), 5.47, 5.59 (1H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 8.22 (1H, s, H-8), 8.85 (1H, s, NH). HPLC retention time 9.15 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96.4% purity at 250 nm).

EXAMPLE 39

5'-Bromo-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

2-Chloro-*N*-(1-piperidinyl)adenosine [WO 93/08206 (Novo Nordisk A/S)] (3.08 g, 8 mmol) was subjected to the same reaction conditions described in Example 24, except that thionyl bromide was substituted for thionyl chloride. The procedure provided the desired 5'-bromo-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine as a foam (0.19 g, 9%) after column chromatography, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.37 (2H, br, piperidine C-H), 1.62 (4H, m, piperidine C-H), 2.80 (4H, br, piperidine C-H), 3.72, 3.82 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.10 (1H, dt, H-4'), 4.17 (1H, dt, H-3'), 4.68 (1H, q, H-2'), 5.50, 5.62 (1H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 8.38 (1H, s, H-8), 9.36 (1H, br, NH). HPLC retention time 11.06 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96.4% purity at 250 nm).

$C_{15}H_{20}N_6BrClO_3.1.3\ H_2O$ requires C, 38.2; H, 4.8; N, 17.8. Found: C, 38.7; H, 4.7; N, 17.3%.

EXAMPLE 40

2-Chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine

Methyl 5-Deoxy-5-fluoro 2,3-*O*-(1-methylethylidene)-D-ribofuranoside

Methyl 2,3-*O*-(1-methylethylidene)-5-*O*-(p-toluenesulfonyl)-D-ribofuranoside (28.7 g, 80 mmol) was dissolved in dry acetonitrile (100 mL). Tetra-*n*-butylammonium fluoride (100 mL, 1.0M in THF) was added dropwise and the reaction mixture was heated at 80°C for 72 h. After cooling to room temperature, the mixture was diluted with dichloromethane (200 mL), washed with water (3 x 50 mL) and dried ($MgSO_4$). Evaporation provided a residue which was purified by flash chromatography eluting with a mixture of ethyl acetate/*n*-heptane (1/3) to give methyl 5-deoxy-5-fluoro-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (13.6 g, 82%) as a clear oil, ^{1}H NMR ($CDCl_3$) d 1.34 (3H, s, CH_3), 1.50 (3H, s, CH_3), 3.35 (3H, s, -OCH_3), 4.29 - 4.48 (3H, m, H-4, H-5$_a$ and H-5$_b$), 4.60 (1H, d, H-3), 4.70 (1H, d, H-2), 4.99 (1H, d, H-1).

1,2,3-Tri-*O*-acetyl-5-deoxy-5-fluoro-D-ribofuranose

Methyl 5-deoxy-5-fluoro-2,3-*O*-(1-methylethylidene)-D-ribofuranoside (5.0 g, 24 mmol) was treated with sulfuric acid (0.02M, 40 mL) and heated at reflux for 4 h. The reaction mixture was cooled, neutralized with barium carbonate to pH 7, filtered and evaporated to an oil. The oil was dried by coevaporation with ethanol, and the residue was dissolved in dichloromethane (50 mL). Acetic anhydride (25 mL) and pyridine (25 mL) were introduced, and the reaction mixture was stirred for 16 h before being poured onto ice (100 mL). The cool suspension was extracted with dichloromethane (3 x 100 mL), and the combined extracts was washed with 2N hydrochloric acid solution (50 mL) and aqueous sodium bicarbonate solution (50 mL). The organic phase was dried ($MgSO_4$), evaporated in vacuo and the residue was purified by flash chromatography, eluting with a mixture of dichloromethane and 10% ammonia in ethanol (97:3) to provide 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-D-ribofuranose (5.3 g, 79%), which crystallized on standing.

Recrystallization from absolute ethanol provided analytically pure material, m.p. 98 - 101°C, ^{1}H NMR ($CDCl_3$) d 2.09 (3H, s, -$OCOCH_3$), 2.10 (3H, s, -$OCOCH_3$), 2.14 (3H, s, -$OCOCH_3$), 4.34 (1H, ddd, H-4), 4.49 (1H, ddd, H-5_a), 4.52 (1H, ddd, H-5_b), 5.36 (1H, d, H-3), 5.46 (1H, dd, H-2), 6.17 (1H, s, H-1).

$C_{11}H_{15}FO_7$ requires C, 47.5; H 5.4. Found: C, 47.7; H, 5.6%.

9-[(2',3'-Di-*O*-acetyl-5'-deoxy-5'-fluoro-D-ribofuranosyl)]-2,6-dichloro-9H-purine

A mixture of the above 1,2,3-tri-*O*-acetyl-5-deoxy-5-fluoro-D-ribofuranose (5.0 g, 18 mmol) and 2,6-dichloropurine (3.4 g, 18 mmol) was heated to 160°C. A catalytic amount of sulphuric acid (one drop) was added at which point a homogeneous melt was obtained. The fusion was continued at 160°C under oil pump vacuum for 0.5 h. After cooling, the reaction mixture was dissolved in chloroform (200 mL) and washed with aqueous sodium bicarbonate (3 x 50 mL) and water (50 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo before purification by flash chromatography. Elution with a mixture of dichloromethane and 10% ammonia in ethanol (98:2) afforded an anomeric mixture of 9-[(2',3'-di-*O*-acetyl-5'-deoxy-5'-fluoro-D-ribofuranosyl)]-2,6-dichloro-9H-purine (4.5 g, 90%) as a gum, ^{1}H NMR (DMSO-d_6)d (a-anomer) 1.84 (3H, s, -$OCOCH_3$), 2.00 (3H, s, -$OCOCH_3$), 4.71 (2H, dd, H-5'a, H-5'b), 5.98 (1H, ddd, H-4'), 5.48 (1H, t, H-3), 5.68 (1H, t, H-2'), 6.73 (1H, d, H-1'), 8.92 (1H, s, H-8); (ß-anomer) 2.05 (3H, s, -$OCOCH_3$), 2.11 (3H, s, -$COCH_3$), 4.50 (1H, ddd, H-4), 4.77 (2H, dd, H-5'$_a$ and H-5$_b$'), 5.61 (1H, t, H-3), 5.89 (1H, t, H-2'), 6.33 (1H, d, H-1), 8.92 (1H, s, H-8).

2',3'-Di-*O*-acetyl-2-chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine

An a/b mixture of 9-[(2',3'-di-*O*-acetyl-5'-deoxy-5'-fluoro-D-ribofuranosyl])-2,6-dichloro-9H-purine (1.24 g, 3.0 mmol), *N,N*-diisopropylethyl amine (0.79 g, 6.1 mmol) and 1-aminopiperidine (0.60 g, 6.0 mmol) were stirred in dioxan (20 mL) for 4 h. The reaction mixture was diluted with dichloromethane (200 mL) and washed with water (2 x 50 mL). After drying over ($MgSO_4$) the

organic phase was evaporated in vacuo and the residue was purified by flash chromatography. Elution with dichloromethane and 10% ammonia in ethanol (98:2) afforded the b-anomer of 2',3'-di-*O*-acetyl-2-chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine (0.40 g, 28%) as a foam. HPLC retention time 14.8 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

The above 2',3'-di-*O*-acetyl-2-chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine (0.38 g, 0.8 mmol) was dissolved in methanolic ammonia (15 mL) and stirred for 1 h. The reaction mixture was evaporated in vacuo and the resultant residue was purified by flash chromatography eluting with dichloromethane and 10% ammonia in ethanol (95:5) to afford 2-chloro-5'-deoxy-5'-fluoro-*N*-(1-piperidinyl)adenosine (1.8 g, 86%) as a white solid, m.p. 199-201°C. ^{1}H-NMR (400MHz, DMSO-d_6) d 1.35 (2H, br, piperidine C-H), 1.52 (4H, br, piperidine C-H), 2.80 (4H, br, piperidine C-H), 4.10 (1H, ddd, H-4'), 4.20 (1H, br, H-3'), 4.51 (1H, br, H-2'), 4.65 (2H, dd, H-5'$_a$ and H-5'$_b$), 5.88 (1H, d, H-1'), 8.28 (1H, s, H-8). HPLC retention time 7.15 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

$C_{15}H_{20}ClFN_6O_3$, $0.75H_2O$ requires C, 45.2; H, 5.4; N, 21.1. Found: C, 45.2; H, 5.2; N, 20.8%.

EXAMPLE 41

2-Chloro-5'-deoxy-5'-fluoro-*N*-benzyloxyadenosine

This compound was prepared by general method A, described in more detail in Example 39 by reacting *O*-benzylhydroxylamine hydrochloride (0.80 g, 5.0 mmol) with 9-[(2',3'-di-*O*-acetyl-5'-deoxy-5'-fluoro-D-ribofuranosyl)]-2,6-dichloro-9H-purine (1.0 g, 2.5 mmol) as described above. The product was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (98:2) giving the intermediate 2',3'-di-*O*-acetyl-2-chloro-5'-deoxy-5'-fluoro-*N*-benzyloxyadenosine (0.2 g, 16%). Deacetylation was performed in methanolic ammonia to afford 2-chloro-5'-deoxy-5'-fluoro-*N*-benzyloxyadenosine as a foam (0.11

g, 89%) after flash chromatography eluting with dichloromethane and 10% ammonia in ethanol (95:5). ^{1}H-NMR (400MHz, DMSO-d_6) d 4.12 (1H, m, H-4'), 4.20 (1H, m, H-3'), 4.53 (1H, m, H-2'), 4.65 (2H, dd, H-5'$_a$ and H-5'$_b$), 5.00 (2H, s, -CH_2-), 5.48, 5.60 (2H, 2d, 2'-and 3'-OH) 5.91 (1H, d, H-1'), 7.30 -7.55 (5H, m, Ar-H), 8.43 (1H, s, H-8), 11.65 (1H, s, N-H). HPLC retention time 14.60 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 96% purity at 250 nm).

EXAMPLE 42

(S)-2-Chloro-5'-*O*-methyl-*N*-(2-(methylmethoxy)-1-pyrrolidinyl)adenosine

Methyl 5-*O*-methyl-2,3-*O*-(1-methylethylidene)-D-ribofuranoside.

Methyl 2,3-*O*-(1-methylethylidene)-D-ribofuranoside (13.3 g, 60 mmol), 2,6-di-t-butyl-4-methyl-pyridine (20.0 g, 100 mmol) and methyl trifluoromethylsulfonate (16.0 g, 100 mmol) were dissolved in dry dichloromethane (150 mL) placed in a closed reactor and heated to 80°C. After cooling, the reaction mixture was poured onto ice (150 mL). After standing, the product was extracted into dichloromethane (2 x 100 mL) and the combined extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography eluting with a mixture of cyclohexane and ethyl acetate (3:1) to afford methyl 5-*O*-methyl-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside (8.0 g, 61%) as an oil. ^{1}H-NMR (400MHz, $CDCl_3$) d 1.30 (3H, s, -CH_3), 1.50 (3H, s, -CH_3), 3.32 (3H, s, -OCH_3), 3.39 (3H, s, -OCH_3), 3.35 - 3.45 (2H, m, H-5$_a$ and H-5$_b$), 4.30 (1H, t, H-4), 4.57 (1H, d, H-3), 4.65 (1H, d, H-2), 4.97 (1H, s, H-1).

1,2,3-Tri-*O*-acetyl-5-*O*-methyl-D-ribofuranose.

5-*O*-Methyl-2,3-*O*-(1-methylethylidene)-D-ribofuranoside (3.0 g, 14 mmol) was dissolved in a mixture of sulfuric acid (0.02M, 100 mL) and ethanol (50 mL) and heated at 80°C for 6 h and stirred for 20 h at 20°C. The reaction mixture was neutralised with aqueous sodium bicarbonate

and concentrated in vacuo. The residual oil was dried and acetylated in a mixture of dichloromethane (100 mL), acetic anhydride (8.5 g, 83 mmol) and triethylamine (16.7 g, 165 mmol) at 20°C for 20 h. The reaction mixture was washed with hydrochloric acid (1M, 50 mL) and water (50 mL). The organic phase was dried ($MgSO_4$) and concentrated to an oil before being purified by flash chromatography. Elution with a mixture of cyclohexane and ethyl acetate (6:4) provided 1,2,3-tri-*O*-acetyl-5-*O*-methyl–β–D-ribofuranose (2.5g, 62%) as an oil.

9-(2',3'-Di-*O*-acetyl-5'-*O*-methyl–β–D-ribofuranosyl)-2,6-dichloro-9H-purine

5-*O*-Methyl-1,2,3-tri-*O*-acetyl-D-ribofuranose (5.0 g, 17 mmol) and 2,6-dichloropurine (3.3 g, 17 mmol) were thoroughly mixed. A catalytic amount of p-toluene sulfonic acid (50 mg) was added and the reaction mixture was heated to 140°C at which point a homogeneous melt was obtained. The fusion was continued at 140°C under oil pump vacuum for 0.5 h. The reaction mixture was dissolved in chloroform (200 mL) and washed with aqueous sodium bicarbonate (3 x 50 mL) and water (2 x 50 mL). The organic phase was dried ($MgSO_4$), evaporated in vacuo and purified by flash chromatography eluting with a mixture of n-heptane and ethyl acetate (1:1) to provide - 9-(2',3'-di-*O*-acetyl-5'-*O*-methyl–β–D-ribofuranosyl)-2,6-dichloro-9H-purine (1.0 g, 14%) as an oil which crystallized from diethyl ether. A mixture of a/ß-anomers (1.2 g, 17%) was also isolated, with mp 59 - 61°C. ^{1}H-NMR (400MHz,$CDCl_3$) d 2.06 (3H, s, -$OCOCH_3$), 3.49 (3H, s, OCH_3), 3.67, 3.72 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.39 (1H, d, H-4'), 5.58 (1H, d, H-3'), 5.75 (1H, t, H-2'), 6.38 (1H, d, H-1'), 8.56 (1H, s, H-8).

$C_{15}H_{16}Cl_2N_4O_6$ requires C, 43.0; H, 3.9; N, 13.4. Found C, 43.1, H, 3.9, N, 13.2%.

(S)-2',3'-Di-*O*-acetyl-2-chloro-5'-*O*-methyl-*N*-[2-(methylmethoxy)-1-pyrrolidinyl]adenosine.

9-(2',3'-Di-*O*-acetyl-5'-*O*-methyl-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.3 g, 3.1 mmol), (S)-*N*-amino-2-(methoxymethyl)pyrrolidine (0.81 g, 6.2 mmol) and triethylamine (0.63 g, 6.2 mmol) were dissolved in dioxan. After stirring for 20 h the reaction mixture was diluted with

dichloromethane (150 mL) and washed with water (2 x 75 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The resultant residue was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (97:3) to afford (S)-2',3'-di-*O*-acetyl-2-chloro-5'-*O*-methyl-*N*-[2-(methyl-methoxy)-1-pyrrolidin-yl] adenosine (0.28 g, 18%) as a foam. ^{1}H-NMR (400MHz, $CDCl_3$) d 1.70 - 2.10 (4H, m, pyrrolidine C-H), 2.05 (3H, s, $-OCOCH_3$), 2.18 (3H, s, $-OCOCH_3$), 2.85 (1H, m, pyrrolidine C-H), 3.10 (1H, br, pyrrolidine C-H), 3.22 (3H, s, $-OCH_3$), 3.35 - 3.70 (8H, m, H-5'$_a$ and H-5'$_b$, $-OCH_3$, pyrrolidine, $-CH_2-$), 4.32 (1H, s, H-4'), 5.55 (1H, d, H-3'), 5.75 (1H, t, H-3'), 6.32 (1H, d, H-1'), 8.17 (1H, s, H-8). HPLC retention time 15.57 min. (gradient elution over 25 min.; 20-80% acetonitrile/0.1% TFA in water).

The above (S)-2',3'-di-*O*-acetyl-2-chloro-5'-*O*-methyl-*N*-[2-(methylmethoxy)-1-pyrrolidinyl]-adenosine (0.26 g, 0.52 mmol) was treated with methanolic ammonia for 1.5 h at room temperature. The crude product was purified by flash chromatography eluting with dichloromethane and 10% ammonia in ethanol (9:1) to give (S)-2-chloro-5'-*O*-methyl-*N*-(2-(methylmethoxy)-1-pyrrolidinyl)adenosine (0.16 g, 72%) as a foam. ^{1}H-NMR (400MHz, DMSO-d_6) d 1.55 (1H, m, pyrrolidine C-H), 1.75 (2H, m, pyrrolidine C-H), 1.97 (1H, m, pyrrolidine C-H), 3.51, 3.59 (1H, ABX, H-5'$_a$ and H-5'$_b$), 4.02 (1H, dd, H-4'), 4.10 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.82 (1H, d, H-1'), 8.32 (1H, s, H-8). HPLC retention time 7.67 min. (gradient elution over 25 min.; 20-80% acetonitrile/0.1% TFA in water).

$C_{17}H_{25}ClN_6O_5$. $0.5H_2O$ requires C, 46.3; H, 5.8; N, 18.5. Found C, 46.7; H, 6.1; N, 18.6%.

EXAMPLE 43

2-Chloro-*N*-methoxy-5'-*O*-methyladenosine

2',3'-Di-*O*-acetyl-2-chloro-*N*-methoxy-5'-*O*-methyladenosine

9-(2',3'-Di-*O*-acetyl-5'-*O*-methyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.364g, 0.87 mmol), *O*-methylhydroxyamine hydrochloride (0.087g; 1.04 mmol) and diisopropylethylamine (0.34 mL, 2.0 mmol) were dissolved in 1,4-dioxan (7.0 mL). The mixture was heated to 50°C under nitrogen for 17 hours. After this time, further methoxylamine hydrochloride (0.087g; 1.04mmol) and diisopropylethylamine (0.340 mL; 2.0mmol) were added and the reaction mixture was heated at 50°C for a further 48 h. The solvent was evaporated and the residue partitioned between ethyl acetate (20 mL) and water (10 mL). The aqueous phase was separated and the organic phase was washed with water (10 mL) and brine (10 mL) before being dried (Na_2SO_4). Evaporation of solvent afforded a foam (0.33 g) which was purified by flash chromatography, eluting with ethyl acetate/heptane (3:2), affording a white foam (0.211 g, 57%). ^{1}H-NMR (200MHz; $CDCl_3$) d 2.05 (3H, s, -$OCOCH_3$), 2.18 (3H, s, -$OCOCH_3$), 3.48 (3H, s, -OCH_3), 3.68 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.00 (3H, s, -N(6)-OCH_3), 4.35 (1H, dd, H-4'), 5.56 (1H, dd, H-3'), 5.76 (1H, dd, H-2'), 6.35 (1H, d, H-1'), 8.28 (1H, s, H-8) and 9.25 (1H, s, exch. NH).

2',3'-Di-*O*-acetyl-2-chloro-*N*-methoxy-5'-*O*-methyladenosine (0.20 g, 0.47 mmol) was dissolved in dry methanol (5 mL) and treated with a methanolic solution of sodium methoxide (3.5 mL, 0.047 mmol). The solution was stirred at room temperature for 24 h. After this time, the pH was adjusted from 9 to 5 using acetic acid (0.02 mL). Solvents were evaporated to afford a pale yellow oil (0.17g) which was purified by flash chromatography. Elution with dichloromethane/ethanol (14:1) gave a white foam (0.115 g, 72%), ^{1}H-NMR (400MHz; DMSO-d_6) d 3.34 (3H, s, -OCH_3), 3.58 (2H, ddd, H-5'$_a$ and H-5'$_b$), 3.78 (3H, s, -N-OCH_3), 4.05 (1H, dd, H-4'), 4.12 (1H, dd, H-3'), 4.52 (1H, dd, H-2'), 5.33 (1H, d, OH) 5.55 (1H, d, OH) 5.76 (1H, d, H-1'), 8.40 (1H, s, H-8), 11.55 (1H, s, NH). HPLC retention time 10.98 min. (gradient elution over 30 min.; 10-80% acetonitrile/0.1%TFA in water). MS (EI): m/e 347 and 345 [M^+], 314 [$(M\text{-}OMe)^+$].

EXAMPLE 44

2-Chloro-5'-deoxy-5'-methylthio-*N*-(1-piperidinyl)adenosine

2-Chloro-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl) adenosine tosylate salt

2-Chloro-*N*-(1-piperidinyl)adenosine (1.5 g, 3.9 mmol), 2,2-dimethoxypropane (0.9 g, 8.6 mmol) and 4-toluenesulfonic acid monohydrate (1.6 g, 18.6 mmol) was stirred in acetone (25 mL) for 72 h. Further 2,2-dimethoxypropane (0.9 g, 8.6 mmol) was added. After a further 24 h the tosylate salt of 2-chloro-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine (1.78 g, 76%) was collected by filtration, m.p. 169-170°C, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.35 (3H, s, -CH_3), 1.46 (2H, br, piperidine C-H), 1.55 (3H, s, -CH_3), 1.75 (4H, m, piperidine -CH), 3.10 (4H, br, piperidine C-H), 3.55 (2H, ABX, H-5$_a$' and H-5'$_b$), 4.29 (1H, m, H-4'), 4.95 (1H, dd, H-3'), 5.30 (1H, dd, H-2'), 6.15 (1H, d, H-1'), 8.72 (1H, s, H-8). HPLC retention time 14.87 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

$C_{25}H_{33}ClN_6O_7S$ requires C, 50.3; H, 5.6; N, 14.1. Found C, 50.7; H, 5.8; N, 13.7%.

2-Chloro-5'-deoxy-5'-methylthio-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine

2-Chloro-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl) adenosine tosylate (0.5 g, 0.84 mmol), tributylphosphine (1.7 g, 8.4 mmol) and dimethyldisulfide (0.4 g, 4.20 mmol) were stirred in dry dimethylformamide (5 mL) under nitrogen for 7 days. The reaction mixture was poured into ice (50 mL) and after standing for 1 h was extracted with dichloromethane (3 x 25 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The crude product was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (95:5) to give 2-chloro-5'-deoxy-5'-methylthio-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine (0.12 g, 31%) as a foam. ^{1}H-NMR (400MHz, $CDCl_3$) d 1.40 (3H, s, -CH_3), 1.45 (2H, m, piperidine C-H), 1.65 (3H, s, -CH_3), 1.70 - 1.85 (4H, m, piperidine C-H), 2.15 (3H, s, -SCH_3),

2.85 (4H, m, piperidine C-H), 4.02, 4.38 (2H, ABX, H-5'$_a$ and H-5'$_b$), 5.05 (1H, dd, H-4'), 5.38 (1H, dd, H-3'), 6.05 (1H, d, H-2'), 6.50 (1H, br, H-1'), 7.83 (1H, s, H-8).

2-Chloro-5'-deoxy-5'-methylthio-*N*-(1-piperidinyl)adenosine

2-Chloro-5'-deoxy-5'-methylthio-2',3'-*O*-(1-methylethylidene)-*N*-(1-piperidinyl)adenosine (0.10 g, 0.22 mmol) was reacted in a mixture of water (2.5 mL) and ethanol (2.5 mL) containing sulfuric acid (0.1 mL) for 10 h at 60°C. The reaction mixture was diluted with dichloromethane (100 mL) and washed with aqueous sodium bicarbonate (2 x 25 mL) followed by water (25 mL). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (95:5) to provide 2-chloro-5'deoxy-5'-methylthio-*N*-(1-piperidinyl)adenosine (0.75 g, 82%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.39 (2H, br, piperidine C-H), 1.62 (4H, m, piperidine C-H), 2.05 (3H, s, -SCH_3), 2.75 - 2.80 (8H, m, H-5'$_a$, H-5'$_b$, piperidine C-H), 4.01 (1H, m, H-4'), 4.10 (1H, m, H-3'), 4.65 (1H, br, H-2'), 6.82 (1H, d, H-1'), 8.39 (1H, s, H-8). HPLC retention time 9.90 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, purity 96% at 250 nm).

EXAMPLE 45

2-Chloro-5'-cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine

Methyl 2,3-*O*-(1-methylethylidene)-5-*O*-(4-nitrobenzenesulfonyl)-β-D-ribofuranoside

Methyl 2,3-*O*-(1-methylethylidene)–β–D-ribofuranose (37 g, 180 mmol) and triethylamine (54.6 g, 540 mmol) were dissolved in dry dichloromethane (100 mL). 4-Nitrobenzenesulfonyl chloride (40.0 g, 180 mmol) was added dropwise at 0°C over 0.5 h. After stirring for 20 h, the reaction mixture was diluted with dichloromethane (1000 mL) and washed with aqueous ammonium chloride (2 x 250 mL) and water (250 mL). After drying ($MgSO_4$) the organic phase was evapor-

ated to dryness in vacuo. Recrystallization from ethyl acetate gave methyl 2,3-*O*-(1-methylethylidene)-5-*O*-(4-nitrobenzenesulfonyl)–β–D-ribofuranoside as a white solid (54.8 g, 85%), m.p. 97-98°C, ^{1}H-NMR (400MHz, $CDCl_3$) d 1.38 (3H, s, $-CH_3$), 1.45 (3H, s, $-CH_3$), 3.26 (3H, s, $-OCH_3$), 4.13 (2H, ABX, H-5_a and H-5_b), 4.32 (1H, t, H-4), 4.53 (1H, d, H-3), 4.61 (1H, d, H-2), 4.95 (1H, s, H-1), 8.12 (2H, d, Ar-H), 8.40 (2H, d, Ar-H).

Methyl 5-cyano-5-deoxy-2,3-*O*-(1-methylethylidene)–β–D-ribofuranoside.

Methyl 2,3-*O*-(1-methylethylidene)-5-*O*-(4-nitrobenzenesulfonyl)–β–D-ribofuranoside (45.3 g, 120 m mol) was added over 1.5 h to a suspension of sodium cyanide (6.8 g, 140 mmol) in dry dimethylformamide (1000 mL). The reaction mixture was heated to 50°C for 3 h before being poured onto ice (500 mL). This mixture was extracted with dichloromethane (3 x 500 mL), the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was distilled under vacuum to give methyl 5-cyano-5-deoxy-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside as an oil (6.3 g, 25%), bp 110-115°C/0.6 mm Hg. ^{1}H-NMR (400MHz, $CDCl_3$) d 1.30 (3H, s, $-CH_3$), 1.48 (3H, s, $-CH_3$), 2.62, 2.70 (2H, ABX, H-5_a and H-5_b), 3.40 (3H, s, $-OCH_3$), 4.45 (1H, s, H-4), 4.61 (1H, d, H-3), 4.63 (1H, d, H-2), 5.00 (1H, s, H-1).

Methyl 2,3-di-*O*-benzoyl-5-cyano-5-deoxy–β–D-ribofuranoside

Methyl 5-cyano-5-deoxy-2,3-*O*-(1-methylethylidene)–β–D-ribofuranoside (18.7 g, 87 mmol) and Amberlyst (H^+ form, 84 g) were mixed and heated at reflux for 24 h. The reaction mixture was filtered and evaporated to a residue which was dissolved in dichloromethane (200 mL), which was washed with water (300 mL). The separated water phase was extracted with ethyl acetate (7 x 200 mL), combined with the earlier organic phase and dried ($MgSO_4$). Evaporation provided the intermediate methyl 5-cyano-5-deoxy–β–D-ribofuranoside (6.85 g) which was dissolved in dichloromethane (200 mL). Benzoyl chloride (24 g, 170 mmol) and triethlamine (34 g, 340 mmol) were introduced and the reaction mixture was stirred for 20 h. at ambient temperature before being washed with 1 N hydrochloric acid solution (2 x 85 mL) and saturated sodium

bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated to a residue which was purified by flash chromatography on silica gel. Elution with a mixture of heptane and ethyl acetate (39:1), increasing polarity to a 9:1 mixture of these solvents provided methyl 2,3-*O*-dibenzoyl-5-cyano-5-deoxy–β–D-ribofuranoside (13.01 g, 40%), ^{1}H-NMR (400MHz, $CDCl_3$) d 3.04, 3.20 (2H, ABX, H-5$_a$ and H-5$_b$), 3.43 (3H, s, -OCH_3), 4.67 (1H, d, H-4), 5.25 (1H, s, H-1), 5.50 - 5.57 (2H, m, H-3 and H-4), 7.4 - 7.95 (10H, 6m, Ar-H).

1-*O*-Acetyl-2,3-di-*O*-benzoyl-5-cyano-5-deoxy-D-ribofuranose

Acetic acid (74.5 mL, 1.3 mol), acetic anhydride (173.8 mL, 1840 mmol) and sulfuric acid (1.7 mL, 32 mmol) were mixed together and methyl 2,3-*O*-dibenzoyl-5-cyano-5-deoxy–β–D-ribofuranoside (13.01 g, 35 mmol) was added. The reaction mixture was stirred for 20 h at ambient temperature before sodium acetate (37 g, 450 mmol) was introduced. After 30 min. stirring the reaction mixture was filtered, the filter pad was washed with ethyl acetate (100 mL) and the filtrate was evaporated to a residue which was coevaporated with toluene (250 mL). The residue was dissolved in a mixture of ethyl acetate (250 mL) and water (250 mL). The ethyl acetate phase was washed with water (2 x 100 mL) and saturated brine (50 mL) before being dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel. Elution with a mixture of hexane and ethyl acetate (9:1), increasing polarity to a 4:1 mixture of these solvents provided the title 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-cyano-5-deoxy–β–D-ribofuranose as a solid single isomer (2.85 g, 20%), mp 124-126°C, ^{1}H-NMR (400MHz, $CDCl_3$) d 2.22 (3H, s, -$OCOCH_3$), 2.92, 3.02 (2H, ABX, H-5$_a$ and H-5$_b$), 4.61 (1H, dt, H-4), 5.70 - 5.80 (2H, 2m, H-2 and H-3), 6.38 (1H, s, H-1) and a mixture of isomers as a gum (7.5 g, 52%).

9-(2',3'-Di-*O*-benzoyl-5'-cyano-5'-deoxy-D-ribofuranosyl)-2,6-dichloro-9H-purine

A mixture of 1-*O*-acetyl-2,3-di-*O*-benzoyl-5-cyano-5-deoxy–β–D-ribofuranose (2.8 g, 6.8 mmol) and 2,6-dichloro-9H-purine (1.36 g, 7.2 mmol) were heated at 145°C for 1.25 h in the presence of a catalytic amount of p-toluenesulphonic acid (0.025 g). The reaction mixture was dissolved in

ethyl acetate (100 mL) and washed with aqueous sodium bicarbonate (100 mL) followed by saturated brine (100 mL). The organic phase was dried ($MgSO_4$), and the solid residue was recrystallised from 2-propanol to provide 9-(2',3'-di-*O*-benzoyl-5'-cyano-5'-deoxy-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (3.3 g, 90%), m.p. 143-145°C, ^{1}H-NMR (400MHz, $CDCl_3$) d 3.15, 3.25 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.74 (1H, dt, H-4'), 5.95 (1H, t, H-3'), 6.12 (1H, t, H-2'), 6.42 (1H, d, H-1'), 7.36 - 8.05 (10H, 4m, Ar-H), 8.40 (1H, s, H-8).

2',3'-*O*-Benzoyl-2-chloro-5'cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine

9-(2',3'-di-*O*-benzoyl-5'-cyano-5'-deoxy-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.75 g, 3.25 mmol), triethylamine (0.9 mL, 6.5 mmol) and 1-aminopiperidine (0.7 mL, 6.5 mmol) were stirred in dioxan (20 mL) for 2 h. The reaction mixture was evaporated and the residue dissolved in dichloromethane (10 mL) and purified by flash chromatography eluting with a mixture of heptane and ethyl acetate (4:1), increasing polarity to a 1:1 mixture of these solvents provided 2',3'-di-*O*-benzyl-2-chloro-5'-cyano-5'deoxy-*N*-(1-piperidinyl)adenosine (1.19 g, 61%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 3.15, 3.31 (2H, ABX, H-5'$_a$ and H-5'$_b$), 4.68 (1H, dd, H-4'), 5.99 (1H, t, H-3'), 6.11 (H, t , H-2'), 6.36 (1H, d, H-1'), 7.36 - 8.00 (10H, m, Ar-H), 8.03 (1H, s, H-8). HPLC retention time 17.26 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water).

2-Chloro-5'-cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine

2-Chloro-2',3'-*O*-benzoyl-5'-cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine (1.5 g, 2.5 mmol) was dissolved in methanolic ammonia (30 mL) and stirred at ambient temperature for 3 h. Following evaporation, the crude product was purified by flash chromatography eluting with a mixture of heptane and ethyl acetate, followed by ethyl acetate alone to provide 2-chloro-5'-cyano-5'-deoxy-*N*-(1-piperidinyl)adenosine as a solid (0.6 g, 61%). Recrystallization from ethyl acetate provided an analytical sample (0.36 g, 37%), m.p. 192-193°C, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.38 (2H, br, piperidine C-H), 1.63 (4H, q, piperidine C-H), 2.81 (4H, br, piperidine C-H), 3.05

(2H, d, H-5'$_a$ and H-5'$_b$), 4.12 (2H, m, H-4'and H-3'), 4.65 (1H, m, H-2'), 5.53, 5.67 (2H, 2d, 2'- and 3'-OH), 5.87 (1H, d, H-1'), 8.37 (1H, s, H-8). HPLC retention time 11.9 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 100% at 250 nm).

$C_{16}H_{20}ClN_7O_3$ requires C, 48.8; H, 5.1; N, 24.9. Found C, 48.9; H, 5.3; N, 24.6%.

EXAMPLE 46

2-Chloro-5'-cyano-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine

This compound was prepared by general method A, described in more detail in Example 44. 2-Chloro-2',3'-*O*-benzoyl-5'-cyano-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine [prepared from 1-amino-6-phenylthiopiperidine (Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic and Medicinal Chemistry Letters, 1993, *3*, 2661-2666) and 9-(2',3'-di-*O*-benzoyl-5'-cyano-5'-deoxy-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine as described in Example 24] (1.5 g, 2.5 mmol) in methanol (20 mL) was treated with methanolic ammonia (5 mL). The reaction mixture was stirred at ambient temperature for 0.75 h. Ethyl acetate (5 mL) was added to the residue on evaporation to provide 2-chloro-5'-cyano-5'-deoxy-*N*-(4-phenylthio-1-piperidinyl)adenosine (0.11 g, 46%) as a solid, m.p. 159-161°C, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.68 (2H, br q, piperidine C-H), 1.98 (2H, m, piperidine C-H), 2.78 (2H, br, piperidine C-H), 3.04 (2H, br d, H-5'$_a$ and H-5'$_b$), 4.11 (2H, m, H-4'and H-3'), 4.63 (1H, m, H-2'), 5.54, 5.68 (2H, 2d, 2'-and 3'-OH), 5.88 (1H, d, H-1'), 7.22 - 7.45 (5H, 3m, Ar-H), 8.38 (1H, s, H-8), 9.49 (1H, s, N-H). HPLC retention time 20.34 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 96% at 250 nm).

$C_{16}H_{20}ClN_7O_3$. 0.7 H_2O. 0.1 EtOAc requires C, 51.4; H, 5.1; N, 18.7. Found C, 51.4; H, 4.9; N, 18.3%.

EXAMPLE 47

2-Chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

Methyl 5-deoxy-2,3-di-*O*-benzoyl-D-ribofuranoside

Methyl 5-deoxy-2,3-*O*-(1-methylethylidene)-D-ribofuranoside (prepared by reduction of methyl 2,3-*O*-(1-methylethylidene)-5'-*O*-(p-toluenesulphonyl)-D-ribofuranoside using lithium aluminium hydride) (4.36 g, 23.2 mmol) was dissolved in methanol (120 mL) and Amberlyst resin (H^+ form, 19 g) was introduced. The mixture was stirred at 80°C for 60 h and filtered. The filter pad was washed with methanol and the filtrate was evaporated to an oily residue. The residue was dissolved in dichloromethane and to this solution was added triethylamine (25.7 g, 185 mmol). Benzoyl chloride (13.08 g, 10.8 mL, 92.8 mmol) was added dropwise over 0.5 h and the reaction mixture was stirred at ambient temperature for 40 h. The reaction mixture was extracted with 0.5 M hydrochloric acid solution (2 x 50 mL) and sodium bicarbonate solution (30 mL) before being dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (4:1), gradually increasing polarity a (1:1) mixture of these solvents, providing the title methyl 5-deoxy-2,3-di-*O*-benzoyl-D-ribofuranoside (6.11 g, 74%), ^{1}H-NMR (400MHz, $CDCl_3$) d 1.50 (3H, d, -CHC$\underline{H}_3$), 3.48 (3H, s, -COCH_3), 4.48 (1H, q), 5.11 (1H, s), 5.46 (1H, t), 5.60 (1H, d), 7.25 - 8.19 (20H, m, Ar-H).

9-(5'-Deoxy-2',3'-di-*O*-benzoyl-β-D-D-ribofuranosyl)-2,6-dichloro-9H-purine

1-*O*-Acetyl-2,3-di-*O*-benzoyl-5-deoxy-D-ribofuranose [prepared from the above methyl 5-deoxy-2,3-di-*O*-benzoyl-D-ribofuranoside by the method described in Lerner, L. Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques, Part Four. Townsend, L.B. and Tipson, R.S., Eds.; John Wiley and Sons, New York, 1991, pp 274 - 280] (1.02 g, 2.65 mmol) and 2,6-dichloro-9H-purine (0.48 g, 2.53 mmol) were mixed thoroughly and heated at 145°C under oilpump vacuum for 2 h. The cooled reaction mixture was dissolved in

dichloromethane (25 mL), evaporated, and coevaporated with toluene (2 x 50 mL). Purification of the residue by flash chromatography provided the title 9-(5'-deoxy-2',3'-di-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.90 g, 58%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.67 (3H, d, -CHC<u>H</u>$_3$), 4.64 (1H, dt, H-4'), 5.72 (1H, t, H-3'), 6.12 (1H, t, H-2'), 6.35 (1H, d , H-1'), 7.31 - 8.05 (10H, m, Ar-H), 8.31 (1H, s, H-8).

2',3'-Di-*O*-benzoyl-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

9-(5'-Deoxy-2',3'-di-*O*-benzoyl-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.46 g, 0.75 mmol) was dissolved in dioxan (10 mL). 1-Aminopiperidine (0.06 mL, 0.90 mmol) and triethylamine (0.16 mL, 1.13 mmol) were added and the reaction mixture was stirred at ambient temperature for 18 h before being evaporated. The residue was treated with water (50 mL) and ethyl acetate (100 mL). The organic phase was separated and washed with water (2 x 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (1:1) to provide the title 2,3-di-O-benzoyl-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine (0.30 g, 69%) as a foam, ^{1}H-NMR (400MHz, $CDCl_3$) 1.48 (2H, br, piperidine C-H), 1.80 (2H, m, piperidine C-H), 2.87 (2H, br, piperidine C-H), 4.57 (1H, dt, H-4'), 5.71 (1H, t, H-3'), 6.07 (1H, t, H-2'), 6.33 (1H, d , H-1'), 7.28 - 8.00 (11H, m, Ar-H and H-8).

2-Chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine

2,3-Di-*O*-benzoyl-2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine (0.30 g, 0.81 mmol) was dissolved in methanol (10 mL) and methanolic ammonia (5 mL) was introduced. The reaction mixture was stirred at ambient temperature for 18 h. and evaporated. The residue was purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (95:5) to provide the title 2-chloro-5'-deoxy-*N*-(1-piperidinyl)adenosine (0.13 g, 43%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.21 - 1.43 (5H, m, piperidine C-H and CHC<u>H</u>$_3$), 1.63 (4H, br q, piperidine C-H), 2.82 (4H, br m, piperidine C-H), 5.79 (1H, d, H-1'), 8.37 (1H, s, H-8), 9.32

(1H, s, N-H). HPLC retention time 6.82 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water).

EXAMPLE 48

2-Chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine

Methyl 5-deoxy-2,3-*O*-(1-methylethylidene)-5-methylene-D-ribofuranoside

Triphenylmethylphosphonium bromide (26.79 g, 75 mmol) was suspended in THF (200 mL) and n-butyllithium (1.7M in hexanes) (42 mL, 71.2 mmol) was introduced. After stirring for 2 h, methyl 5-deoxy-5-oxo-2,3-*O*-(1-methylethylidene)-D-ribofuranoside (prepared by oxidation of 1-*O*-methyl-2,3-*O*-(1-methylethylidene)-D-ribofuranoside using the method described in Ranganathan, R.S., Jones, G.H. and Moffatt, J.G., Journal of Organic Chemistry, **1974**, *39(3)*, 290-298) (5.06 g, 25 mmol) in THF (50 mL) was added dropwise. The reaction mixture was heated for 2 h at 50°C and cooled. A mixture of water (10 mL) and THF (90 mL) were added carefully under a stream of nitrogen. Diethyl ether (250 mL) and water (250 mL) were introduced. The aqueous phase was washed with diethyl ether (250 mL) and the combined organic extracts were washed with saturated brine (150 mL) and dried ($MgSO_4$). The residue on evaporation was purified by flash chromatography eluting with a mixture of cyclohexane and ethyl acetate (19:1), increasing polarity to a mixture of heptane and ethyl acetate (9:1) provided the desired methyl 5-deoxy-2,3-*O*-(1-methylethylidene)-5-methylene-D-ribofuranoside (3.6 g, 72%) as a gum, ^{1}H-NMR (400MHz, $CDCl_3$) d 1.32, 1.50 (6H, 2s, $C(CH_3)_2$), 3.36 (3H, s, -$COCH_3$), 4.64 (1H, s), 4.65 (1H, d), 5.00 (1H, s), 5.15 (1H, d), 5.26 (1H, d), 5.83 - 5.92 (1H, m).

Methyl 2,3-di-*O*-benzoyl-5-deoxy-5-methylene-D-ribofuranoside

Methyl 5-deoxy-2,3-*O*-(1-methylethylidene)-5-methylene-D-ribofuranoside (5.65 g, 28.2 mmol)

was dissolved in methanol (250 mL) and Amberlyst resin (H^+ form, 30 g) was introduced. The mixture was stirred at ambient temperature for 40 h and was filtered. The filter pad was washed with methanol and the filtrate was evaporated to an oily residue. The residue was dissolved in dichloromethane and to this solution was added benzoyl chloride (8.47 g, 7.0 mL, 60 mmol) and triethylamine (6.49 g, 8.94 mL, 66 mmol) and the reaction mixture was stirred at ambient temperature for 18 h. The reaction mixture was extracted with 0.5 M hydrochloric acid solution (2 x 100 mL) and water (100 mL) before being dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (29:1), gradually increasing polarity to a (4:1) mixture of these solvents, providing the title methyl 2,3-di-*O*-benzoyl-5-deoxy-5-methylene-D-ribofuranoside (1.66 g, 26%), ^{1}H-NMR (400MHz, $CDCl_3$) d 3.50 (3H, s, -$COCH_3$), 4.75 - 4.82 (1H, m), 5.16 (1H, s), 5.30 (1H, d), 5.45 (1H, d), 5.61 (1H, d), 5.94 - 6.09 (1H, m).

9-(5'-Deoxy-2',3'-di-*O*-benzoyl-5'-methylene-β-D-ribofuranosyl)-2,6-dichloro-9H-purine

1-*O*-Acetyl-2,3-di-*O*-benzoyl-5-deoxy-5-methylene-D-ribofuranose [prepared from the above methyl 2,3-di-*O*-benzoyl-5-deoxy-(1-methylethylidene)-5-methylene-D-ribofuranoside by the method described in Lerner, L. Nucleic Acid Chemistry: Improved and New Synthetic Procedures, Methods and Techniques, Part Four. Townsend, L.B. and Tipson, R.S., Eds.; John Wiley and Sons, New York, 1991, pp 274 - 280] (4.2 g, 10.6 mmol) and 2,6-dichloro-9H-purine (2.0 g, 10.6 mmol) were suspended in dichloromethane (25 mL) and evaporated to a residue which was heated at 150°C under oilpump vacuum for 1.5 h. The cooled reaction mixture was dissolved in dichloromethane (25 mL), evaporated, and coevaporated with toluene (2 x 50 mL). Purification of the residue by flash chromatography eluting with a mixture of heptane and ethyl acetate (9:1), increasing polarity to a mixture of heptane and ethyl acetate (4:1) provided the title 9-(5'-deoxy-2',3'-di-*O*-benzoyl-5'-methylene-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (3.98 g, 71%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 4.98 (1H, d), 5.48 (1H, d), 5.58 (1H, d), 5.91 (1H, t), 6.16 (1H, t , H-2'), 6.22 (1H, m), 6.44 (1H, d, H-1'), 7.34 - 8.08 (10H, m, Ar-H), 8.34 (1H, s, H-8). HPLC retention time 15.51 min. (gradient elution over 30 min.; 20-80%

acetonitrile/0.1% TFA in water).

2',3'-Di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine

9-(5'-Deoxy-2',3'-di-*O*-benzoyl-5'-methylene-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.3 g, 0.57 mmol) was dissolved in dioxan (20 mL). 1-Aminopiperidine (0.066 g, 0.63 mmol) and triethylamine (0.087 g, 0.12 mL, 0.86 mmol) were added and the reaction mixture was stirred at ambient temperature for 40 h and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (4:1), gradually increasing polarity to a (1:1) mixture of these solvents, to afford the title 2,3-di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine (0.28 g, 83%), ^{1}H-NMR (400MHz, $CDCl_3$) d 4.93 (1H, dt), 5.43 (1H, dd), 5.56 (1H, d), 5.89 (1H, t), 6.10 (1H, t , H-2'), 6.21 (1H, m), 6.42 (1H, d, H-1'), 7.33 - 8.05 (10H, m, Ar-H).

2-Chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine

2,3-Di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine (0.28 g, 0.47 mmol) was dissolved in methanolic ammonia (10 mL) and stirred at ambient temperature for 18 h. The reaction mixture was evaporated and purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (95:5) to provide the title 2-chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine (0.081 g, 45%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.30 - 1.45 (2H, br m, piperidine C-H), 1.62 (4H, br q, piperidine C-H), 2.84 (4H, br, piperidine C-H), 4.07 (1H, dt, H-3'), 4.32 (1H, q, H-2'), 4.58 (1H, m, H-4'), 5.20 (1H, dd, C=C-H), 5.30 (1H, d, C=C-H), 5.40, 5.56 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 6.07 (1H, m, C=C-H), 8.36 (1H, s, H-8), 9.34 (1H, s, N-H). HPLC retention time 9.35 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 99.5% at 250 nm).

EXAMPLE 49

2-Chloro-5'-deoxy-5'-methylene-*N*-(4-phenylthio-1-piperidinyl)adenosine

2',3'-Di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-(4-phenylthio-1-piperidinyl) adenosine, prepared as described in Example 48 from 9-(5'-deoxy-2',3'-di-*O*-benzoyl-5'-methylene-β-D-ribofuranosyl)-2,6-dichloro-9H-purine (1.0 g, 1.9 mmol) and 1-amino-4-phenylthiopiperidine (0.44 g, 2.1 mmol), was dissolved in methanol (20 mL) and sat. methanolic ammonia (2.5 mL) was introduced. The reaction mixture was stirred at ambient temperature for 18 h, evaporated and purified by flash chromatography eluting with a mixture of dichloromethane and ethanol (50:1) to provide the title 2-chloro-5'-deoxy-5'-methylene-*N*-(4-phenylthio-1-piperidinyl)adenosine (0.27 g, 29%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.70 (2H, br q, piperidine C-H), 1.99 (2H, br d, piperidine C-H), 2.77 (2H, br m, piperidine C-H), 3.06 (2H, br m, piperidine C-H), 4.07 (1H, q, H-3'), 4.32 (1H, dt, H-2'), 4.58 (1H, m, H-4'), 5.20 (1H, dd, C=C-H), 5.29 (1H, d, C=C-H), 5.39, 5.56 (2H, 2d, 2'-and 3'-OH), 5.86 (1H, d, H-1'), 6.07 (1H, m, C=C-H), 7.23 - 7.45 (5H, 3 m, Ar-H), 8.36 (1H, s, H-8), 9.34 (1H, s, N-H). HPLC retention time 13.46 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 100% at 250 nm).

EXAMPLE 50

2-Chloro-5'-deoxy-*N*-methoxy-5'-methyleneadenosine

2',3'-Di-*O*-benzoyl-2-chloro-5'-deoxy-*N*-methoxy-5'-methyleneadenosine (0.2 g, 0.4 mmol), prepared by the method described in Example 48 from 9-(5'-deoxy-2',3'-di-*O*-benzoyl-5'-methylene-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine (0.5 g, 2.0 mmol) and *O*-methylhydroxlamine hydrochloride (0.167 g, 2.0 mmol), was treated with methanolic ammonia (10 mL) and stirred at ambient temperature for 18 h. The reaction mixture was evaporated and purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in

ethanol (19:1) to provide the title 2-chloro-5'-deoxy-*N*-methoxy-5'-methyleneadenosine (0.03 g, 9%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 3.79 (3H, s, -CH_3), 4.08 (1H, q, H-3'), 4.33 (1H, dt, H-2'), 4.61 (1H, m, H-4'), 5.20 (1H, dd, C=C-H), 5.31 (1H, d, C=C-H), 5.42, 5.59 (2H, 2d, 2'-and 3'-OH), 5.89 (1H, d, H-1'), 6.08 (1H, m, C=C-H), 8.44 (1H, s, H-8), 11.58 (1H, s, N-H). HPLC retention time 7.09 min. (gradient elution over 30 min; 25-45% acetonitrile/0.1% ammonium sulfate in water), purity 98.6% at 250 nm).

EXAMPLE 51

2-Chloro-5'-deoxy-5'-methylene-*N*-(1-piperidinyl)adenosine

2,3-Di-*O*-benzoyl-2-chloro-5'-deoxy-5'-methylene-*N*-cyclopentyladenosine (prepared by reaction of 9-(5'-deoxy-2',3'-di-*O*-benzoyl-5'-methylene-ß-D-ribofuranosyl)-2,6-dichloro-9H-purine (see Example 48) with cyclopentylamine) (0.30 g, 0.52 mmol) was dissolved in methanolic ammonia (10 mL) and stirred at ambient temperature for 18 h. The reaction mixture was evaporated and purified by flash chromatography eluting with a mixture of dichloromethane and 10% ammonia in ethanol (39:1) to provide the title 2-chloro-5'-deoxy-5'-methylene-*N*-cyclopentyladenosine (0.051 g, 27%) as a foam, ^{1}H-NMR (400MHz, DMSO-d_6) d 1.48 - 2.04 (8H, 3 br m, cyclopentyl C-H), 4.08 (1H, q, H-3'), 4.32 (1H, dt, H-2'), 4.42 (1H, m, -HN-C-H), 4.59 (1H, m, H-4'), 5.19 (1H, dd, C=C-H), 5.30 (1H, d, C=C-H), 5.40, 5.55 (2H, 2d, 2'-and 3'-OH), 5.85 (1H, d, H-1'), 6.08 (1H, m, C=C-H), 8.34 (1H, s & br s, H-8 and N-H).

EXAMPLE 52

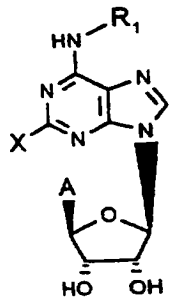
5'-Deoxy-2,5'-dichloro-*N*-(4-phenylthio-1-piperidinyl)adenosine

This compound was prepared by the method described in Example 24. 2-Chloro-*N*-(4-phenylthiocyclohexyl)adenosine (prepared from 4-hydroxycyclohexlamine by the general methods laid out in Knutsen, L.J.S., Lau, J., Sheardown, M.J., Thomsen, C.; Bioorganic

and Medicinal Chemistry Letters, **1993**, *3*, 2661-2666) (0.2 g, 0.44 mmol) was subjected to the reaction conditions described above, and the residue on evaporation was purified by flash chromatography on silica gel eluting with a mixture of heptane and ethyl acetate (4:1), gradually increasing polarity to a (19:1) mixture of ethyl acetate and methanol to afford the title 5'-deoxy-2,5'-dichloro-*N*-(4-phenylthiocyclohexyl)adenosine (0.08 g, 38%), ^{1}H-NMR (400MHz, $CDCl_3$) d 1.20 - 1.30 (2H, t, cyclohexyl C-H), 1.80 - 2.05 (6H, br m, cyclohexyl C-H), 3.75 - 3.84 (2H, m, H-5'$_a$ and H-5'$_b$), 5.96 (1H, d, H-1'), 7.19 - 7.33 (3H, m, Ar-H), 7.41 (2H, d, Ar-H), 7.99 (1H, s, H-8), 8.29 (1H, s, N-H). HPLC retention time 9.1 min. (gradient elution over 30 min.; 20-80% acetonitrile/0.1% TFA in water, 100% purity at 250 nm).

Claims.

1. A method of treating disorders related to cytokines in mammals comprising administering to a mammal in need thereof an effective amount of a compound of the general formula (I), or a pharmaceutically acceptable salt thereof:



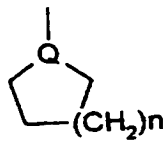
(I

wherein

X represents hydrogen, halogen, amino, perhalomethyl, cyano, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino or phenyl;

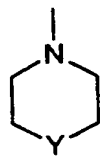
A is hydroxymethyl, methyl, chloromethyl, bromomethyl, fluoromethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl;

R_1 is selected from the groups consisting of



(a)

wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy- C_{1-6} -alkyl, phenylthioalkyl or



(b)

wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

R^1 is $-NR^2R^3$ or $-YR^4$,
wherein Y is oxygen;
R^2 is C_{1-6}-alkyl;
R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;
R^4 is straight-chain C_{1-6}-alkyl, branched C_{3-8}-alkyl, C_{2-8}-alkenyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

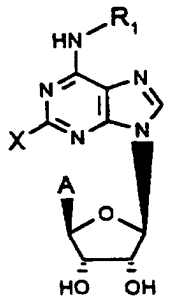
2. A method according to claim 1 wherein said disorder is an autoimmune disorder, inflammation, arthritis, type I or type II diabetes, multiple schlerosis, stroke, osteoporosis, septic shock or menstrual complications.

3. A method according to claim 2 wherein the disorder is type I or type II diabetes, preferably type II diabetes.

4. A method according to any of the preceding claims comprising administering a compound of the general formula (I) wherein R^1 is $-OR^4$, wherein R^4 is straight-chain C_{1-6}-alkyl, branched C_{3-8}-

alkyl, C_{2-8}-alkenyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

5. A compound characterised by the general formula (I), or a pharmaceutically acceptable salt thereof:



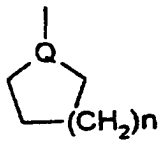
(I

wherein

X represents phenyl;

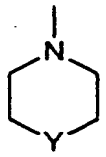
A is hydroxymethyl, methyl, chloromethyl, bromomethyl, fluoromethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl;

R_1 is selected from the groups consisting of



(a)

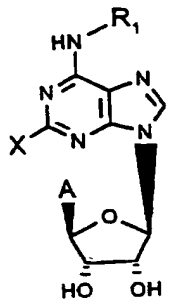
wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy- C_{1-6}-alkyl, phenylthioalkyl or

(b) 

wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

R^1 is $-NR^2R^3$ or $-YR^4$,
wherein Y is oxygen;
R^2 is C_{1-6}-alkyl;
R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;
R^4 is straight-chain C_{1-6}-alkyl, branched C_{3-8}-alkyl, C_{2-8}-alkenyl or C_{3-8}-cycloalkyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

6. A compound characterised by the general formula (I), or a pharmaceutically acceptable salt thereof:



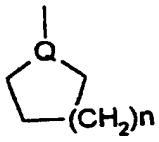
(I

wherein

X represents hydrogen, halogen, amino, perhalomethyl, cyano, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylamino or phenyl;

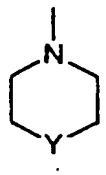
A is hydroxymethyl, methyl, chloromethyl, bromomethyl, fluoromethyl, cyanomethyl, aminomethyl, vinyl, methylthiomethyl or methoxymethyl;

R_1 is selected from the groups consisting of



(a)

wherein Q is nitrogen or carbon, n is 1 to 3 and where the group (a) may be optionally substituted with one or two C_{1-6}-alkyl groups, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenylsulphonyl, phenylthio, hydroxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy- C_{1-6}-alkyl, phenylthioalkyl or

(b) 

wherein Y is O, S or NZ, where Z is H, C_{1-6}-alkyl or phenyl, and where the group (b) may be optionally substituted with C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, phenoxy, phenyl, C_{1-6}-alkoxy or C_{1-6}-alkoxy-C_{1-6}-alkyl, or

R^1 is $-NR^2R^3$ or $-YR^4$,

wherein Y is oxygen;

R^2 is C_{1-6}-alkyl;

R^3 is phenyl or C_{1-6}-alkyl which may be substituted by phenyl or phenoxy;

R^4 is branched C_{3-8}-alkyl or C_{2-8}-alkenyl, which may be substituted by phenyl or phenoxy which in turn may be substituted with nitro, halogen or amine.

7. A pharmaceutical composition comprising as active component a compound according to claim 5 or 6 and a pharmaceutically acceptable carrier or diluent.

8. The use of a compound as defined in claim 1, 4, 5 or 6 for the manufacture of a pharmaceutical composition for treating disorders related to cytokines in humans.

9.The use of a compound as defined in claim 1, 4, 5 or 6 for the manufacture of a pharmaceutical composition for treating autoimmune disorders, inflammation, arthritis, type I or type II diabetes, multiple schlerosis, stroke, osteoporosis, septic shock or menstrual complications.

10.The use of a compound as defined in claim 1, 4, 5 or 6 for the manufacture of a pharmaceutical composition for treating type I or type II diabetes, preferably type II diabetes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00108

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/70, C07H 19/167
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0490818 A1 (SANDOZ LTD.), 17 June 1992 (17.06.92), claims ---	1-10
X	EP 0322242 A2 (GLAXO GROUP LIMITED), 28 June 1989 (28.06.89) ---	1-10
X	Molecular and Cellular Biochemistry, Volume 144, 1995, Lesley Heseltine et al, "Adenosine effects upon insulin action on lipolysis and glucose transport in human adipocytes" page 147 - page 151 ---	1-10

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 June 1997	22 -07- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00108

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A		1-4,8-10
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PCT/DK 97/00108

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